IN THE UNITED STATES DISTRICT COURT FOR THE

SOUTHERN DISTRICT OF WEST VIRGINIA, HUNTINGTON DIVISION

BEFORE THE HONORABLE ROBERT C. CHAMBERS, JUDGE

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CLAUDE R. KNIGHT and CLAUDIA STEVENS, individually and as personal representatives of the Estate of BETTY ERLENE KNIGHT, deceased,

Plaintiffs,

vs. No. 3:15-CV-06424

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC., Volume 2
Pages 122 through 400

Defendant.
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REPORTER'S TRANSCRIPT OF PROCEEDINGS

JURY TRIAL

THURSDAY, OCTOBER 4, 2018, 9:00 A.M.

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(Appearances continued next page...)

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CLAUDE R. KNIGHT, Plaintiff

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HUNTINGTON, WEST VIRGINIA

THURSDAY, OCTOBER 4, 2018, 9:10 A.M.

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(Jury not present.)

THE COURT: Good morning.

MR. MOSKOW: Good morning, Your Honor.

MS. JONES: Good morning, Your Honor.

THE COURT: Before we bring the jury in, the defense filed a motion seeking to preclude the plaintiffs from offering a particular set of opinions from Dr. Plunkett concerning the 75-milligram dose label. I'll give each side just like two minutes to argue.

MS. JONES: Thank you, Your Honor, and I will be very brief.

Our motion is a narrow one. We are not asking to preclude Dr. Plunkett from talking about the 75-milligram at all. To the extent that she's disclosed comments or opinions about the 75-milligram in her report or her deposition testimony, we don't have an issue with that.

We understand --

THE COURT: Was she deposed for this case?

MS. JONES: She was deposed generally for the litigation. I don't think there was ever a separate litigation for -- or a separate deposition for Knight specifically.

THE COURT: At the time she was deposed, the Knight case was one of the pending cases, though?

MR. CHILDERS: That's correct. This was either the first or second case that had been filed.

THE COURT: All right. Is your microphone on?

MR. CHILDERS: I'm sorry. The answer is yes, Your Honor.

THE COURT: All right. Go ahead.

MS. JONES: And so we're really only seeking to exclude a specific opinion concerning the labeling that we understand that Dr. Plunkett intends to offer today, which is that the labeling was somehow deficient because it didn't inform patients that the 75-milligram dose had not been tested in patients in a clinical trial setting or that Pradaxa had not been tested in patients who had severe renal impairment.

That just doesn't appear in her report. She never said it at her deposition. She's been a live witness at three Pradaxa trials all about the 150, but there has never been any mention of that opinion. And certainly Dr. Plunkett has the ability, as is reflected in her report, to be very direct and very specific about what her opinions are.

And the response that was filed by plaintiffs this morning, I think the five pages or so of excerpts from her

report really prove our point. Most of those references include no specificity with regard to a warning about the 75-milligram dose and the testing of the 75-milligram dose.

We are not proposing that she not be able to say the things that are in her report. But she has never testified or offered the opinion that the label was inadequate because it didn't say that it was not tested in patients with severe renal impairment. She has never offered the opinion that the label was inadequate because it didn't say that Pradaxa was never tested in the 75-milligram dose in human patients. Those are new opinions.

To the extent that she is permitted to offer them today, we view that as being prejudicial, and so we're objecting to that testimony on that limited basis.

THE COURT: I'll give you a couple of minutes to respond.

MR. MOSKOW: Thank you, Your Honor, very briefly.

We believe, first of all, the motion is untimely. That when defendants moved en masse to preclude plaintiffs' experts, they specifically moved to preclude labeling opinions of three of the experts and did not seek to preclude any labeling opinions by Dr. Plunkett.

THE COURT: Of course, in their motion they say that they weren't aware that you were going to elicit these opinions until Mr. Childers' opening statement made it clear

that that would be the case.

MR. MOSKOW: I appreciate that, Your Honor. I think -- with all due respect, I think that is disingenuine.

This case has always been about the 75-milligram dose. Among the only issues that is not contested in this case is that, under West Virginia law, the warning was required to be delivered directly to the patient.

While Dr. Plunkett has been disclosed in a number of Pradaxa cases, most of them are the 150, but there are specific references to the 75-milligram dose in this report and the fact that it was untested. And as reflected in our papers, that's an opinion that she gave as being very unusual. She was not asked about why that was unusual. She was not asked at her deposition as to the consequences of it not being tested in people.

And finally, Your Honor -- again, I think, you know, we responded as quickly as we could in our papers that were filed this morning, particularly given the timing of this motion, but I want to be clear.

If the Court were to go to page 7 of our response, you'll see that on page 8 of the report, bullet point two, she specifically says the discussion in the label is incomplete with respect to the known effects of a variety of patient demographics on the risk of bleeding events in particular. And they had an opportunity at the deposition

to ask her what are those patient demographics that you're most concerned about. And she would have responded among the things that I am most concerned about is that the product was never tested on patients with creatinine clearance below 30. The 75-milligram dose was never tested, and it's now being sold to those patients without telling them that that's a fact.

THE COURT: And in your response, you purport to quote from a number of paragraphs of her report.

Those are all taken directly from --

MR. MOSKOW: They are, Your Honor. And I have copies of those for the Court and for counsel if you would like.

THE COURT: I don't need to see them. Further, I think I've already seen her report anyway.

MR. MOSKOW: You have, Your Honor.

THE COURT: I'm going to deny the motion.

First, it's been clear all along that this is a case in which the plaintiffs' allegations focus on the 75-milligram dose of Pradaxa. The criticisms offered by Dr. Plunkett in her report are broad in the sense that they don't particularize the dosage in every instance where she offers an opinion, but those opinions are broad enough that they surely encapsulate opinions about the 75 dose.

Then, in particular, paragraph 66, which plaintiffs

quote from, includes a statement italicized in what they've submitted -- I suspect it wasn't italicized in the original report, but it says, quote: It's unusual, however, for such data -- that means the RE-LY data -- to form the basis of an approval decision of an untested dose, 75-milligram Pradaxa.

So, you know, I appreciate that in a case like this both sides are using proof and evidence developed for a number of different cases and are then presenting those cases here. Even so, counsels' obligation is to provide the expert report -- they did so here -- on behalf of Dr. Plunkett. I don't read that report as in any sense excluding or restricting the opinions. And it's been known that this is the 75-milligram dose, the prescription that is at issue here, so I think the report clearly was intended to cover the dosage that is uncontested as the fact here.

And then when I see statements like the one here that I just quoted from, it seems to me if the defendant questioned whether or not this expert was going to opine that the data was insufficient that there wasn't any testing for the 75-milligram dosage, that they could have pursued this by a supplemental deposition just for this case.

So I deny the motion.

Are we ready to proceed?

MR. MOSKOW: Thank you, Your Honor.

Dr. Plunkett is in the courtroom. We're good to go.

THE COURT: All right. Let's bring the jury in.

(Jury present.)

THE COURT: As the jury is coming out, I had forgotten, my clerk mentioned that you have another list of exhibits that are being introduced.

MR. CHILDERS: Yes, sir.

THE COURT: We've been trying to do that without interrupting the flow of evidence. So even though the jury is coming in, do you want to go ahead and complete that as they are being seated?

MR. CHILDERS: Sure, Your Honor.

THE COURT: Good morning.

MR. CHILDERS: I apologize, it's a list of numbers.

From the Friedman deposition, plaintiffs move in Trial Exhibit Nos. 93, 1075, 288, 38, 36, 671, 684, 1577, 279, 6, 310, 1045, 167, 919, 151, 1046, 543, and 816.

THE COURT: Any objection to the admission of those exhibits into evidence?

MS. JONES: No, Your Honor. Thank you.

THE COURT: All right. They're admitted.

(PLAINTIFFS' EXHIBITS 6, 36, 38, 93, 151, 167, 279, 288, 310, 543, 671, 684, 816, 919, 1045, 1046, 1075, and 1577 ADMITTED INTO EVIDENCE.)

THE COURT: And just to keep it straight in my mind, and maybe for the jury, too. So these are the exhibits that

are now admitted into evidence that were referred to in the deposition, but may be under a different number or identification in the deposition?

MR. CHILDERS: That's correct, Your Honor.

THE COURT: All right.

MR. CHILDERS: And that was for Dr. Friedman's deposition, the first one we heard yesterday.

THE COURT: All right. Very good.

Call your next witness.

MR. CHILDERS: I'm sorry. They have some as well.

THE COURT: I'm sorry.

MS. JONES: We just have two for Dr. Friedman, Your Honor, and I believe we also have exhibits for Ms. Kliewer that we need to read in as well.

THE COURT: Okay. Let's do all this now.

MS. JONES: So for the defense, we just have two exhibits, Trial Exhibit 5881 and 5980 for Dr. Friedman.

THE COURT: Any objection?

MR. CHILDERS: No objection, Your Honor.

THE COURT: They are admitted.

(DEFENDANT'S EXHIBITS 5881 and 5980 ADMITTED INTO EVIDENCE.)

MR. CHILDERS: For Ms. Kliewer's depositions, plaintiffs move into evidence Exhibits 1419, 1673, 387, 72, 321, 280, 188, 1145, 141, 144, 494, 482, 80, and 153.

THE COURT: Any objection?

MS. JONES: No objection, Your Honor.

THE COURT: Those are admitted.

(PLAINTIFF'S EXHIBITS 72, 80, 141, 144, 153, 188, 280, 321, 387, 482, 494, 1145, 1419, and 1673 ADMITTED INTO EVIDENCE.)

THE COURT: And then you have corresponding exhibits?

MS. JONES: Yes, Your Honor. On behalf of the defense, we move in Trial Exhibits 5020, 5021, 5061, 5062, 5138, 5151, 5881 and 5884.

MR. CHILDERS: No objection, Your Honor.

THE COURT: They're admitted as well.

MS. JONES: Thank you, Your Honor.

(DEFENDANT'S EXHIBITS 5020, 5021, 5061, 5062, 5138, 5151, 5881, and 5884 ADMITTED INTO EVIDENCE.)

THE COURT: All right. Call your next witness.

MR. MOSKOW: Good morning, Your Honor. Good morning, Ladies and Gentlemen.

The plaintiff calls Laura Plunkett.

THE COURT: All right. Dr. Plunkett, if you will step up here, my clerk will administer the oath, and then you can take the stand.

THE CLERK: Please raise your right hand.

LAURA PLUNKETT, Ph.D., PLAINTIFFS' WITNESS, SWORN

THE WITNESS: I do.

THE CLERK: Have a seat.

MR. MOSKOW: Your Honor, I have binders for the Court and for the witness and defense that we will be using today.

THE COURT: Wonderful.

MR. MOSKOW: Thank you.

Good morning again, Ladies and Gentlemen.

DIRECT EXAMINATION

BY MR. MOSKOW:

Q. Good morning, Dr. Plunkett.

A. Good morning.

Q. Could you introduce yourself to the jury, please?

A. Sure. My name is Laura Massey Plunkett, and I'm a consultant, and I come from -- I live right now in Houston, Texas.

Q. Okay. I called you doctor when I introduced you to the jury and the Court.

What kind of doctor are you?

A. I'm a -- I have a Ph.D. degree in pharmacology, and I'm board certified in toxicology.

Q. And what does it mean to have a Ph.D. in pharmacology? How many years of college is that?

A. So it's eight years of college, four undergraduate and four in graduate school.

Q. And you said you're board certified in toxicology.
What does that mean?
A. That's a process where you take an exam, essentially pass a test that tests your knowledge in the area of toxicology. And that was done after -- after my degree. So my degree was granted in 1984 with my Ph.D., and then I was board certified in toxicology in 1993.
Q. We've been talking about pharmaceuticals. Pharmacology sounds similar.
Can you explain to the jury what pharmacology has to do with drugs?
A. Sure.
Pharmacologists like myself study the way drugs affect your body, how do they produce the things that you want. So, for example, in this case how does a drug cause your blood to thin. How does it produce what's called the anticoagulant effect, stops the blood from clotting. There are all kinds of drugs I've studied in my life, and we are here to talk about that one specific class today.
Q. How is that different from toxicology or the certified toxicologist that you just told us about?
A. So drugs have both desired effects, the things that you want them to produce, and then they also have toxic effects or things you don't want to see.
As a toxicologist, when you're using those kinds of

tools -- toxicology is a tool or those kinds of things that you learn in school or in books or through your training. You are actually studying what happens when drugs are producing those undesired or those toxicities. So in this case it would be -- the toxicity would be bleeding, whereas the benefit or the thing that you want the drug to produce would be producing a prevention of stroke.

So pharmacologists can study both ends of the spectrum, but the board certification focuses more deeply on just those things about the mechanisms that underlie how you get to these toxic effects, the chemicals in the -- either humans, but also in animals. And also toxicologists study how things affect the environment as well.

Q. Is there anything unusual about the pharmacology of Pradaxa that also implicates or also makes toxicology particularly important?

A. Yes.

Q. And what is that?

A. So Pradaxa is, as I mentioned, an anticoagulant. And what is different about these anticoagulants, these drugs like Pradaxa that thin the blood, these drugs are ones that the dose you take that produces the pharmacologic effect, the thing you want to happen, also is a dose that can produce serious and life-threatening toxicity.

So most drugs when you take them at the dose that you're

given by the doctor, or that you buy over the counter from the pharmacy, for example, you have to take multiples, two pills, three pills, four pills to get to life-threatening toxicities, things that could actually lead to death. This is different for this drug, for this class of drugs. This can happen by taking the actual dose that the doctor tells you to take, so the prescribed dose. It's a very delicate balance for you to move as a person from the drug being safe and the drug producing a life-threatening bleed.

Q. And we'll talk more about that in a moment. I want to come back to the first thing you said to the jury. You said that you are a consultant.

What does that mean?

A. It means I work with clients -- I work for myself, but I work with clients on a variety of different issues, not just one thing. So, for example, I used to be -- I used to work in academics. I used to be a professor, and I would teach, and teaching and working in my lab were how I would describe what I did.

Today, as a consultant, I work on issues for my clients. I help them solve problems. I help them, ah, prepare for meetings. Or I help them prepare things that are submitted to the Food and Drug Administration as part of a process that they're under, getting either approval or there is a problem with their compound or a problem with their product.

So consultants do what I call issue solving, and I do it -- solve those issues applying science because that's what my background is.

Q. And you mentioned that there is some interaction with the FDA, and I'll go into more detail about that in a few moments.

But can you just briefly explain to the jury what it is you do with the FDA?

A. So many of the projects or the clients I work with make a product or have been exposed to a product that is regulated or there's an oversight from the FDA. So that means they are either going to be drugs like Pradaxa. They could be an over-the-counter drug like Tylenol. They could be a medical device. I work on projects with people that work with heart valves, metal implants for hip replacement, those kinds of things.

I also work on products that are called dietary supplements. So if you go to a General Nutrition Store, the GNC, and you buy a vitamin or you buy a product that is an amino -- well, it's a particular product that is not actually one that is sold by a drug company, but sold by a company that manufactures things. Herbs are considered supplements, so I help with those kinds of projects. Cosmetics is another type of product that I work on because those are also regulated by the FDA.

So I work with different clients on a variety of different projects, but the common issue is always something to do with what are the benefits or the things that you want this product to do in the person that's taking it. Or often I'm working on projects like this, and that has to do with what are the toxicities or what are the harmful or the safety issues associated with use of that product.

Q. When you say a project like this, what do you understand the project you're here to talk about with the jury today?

A. In this case, I was asked to look at the issues related to both the benefits or the things that Pradaxa does that you want to do, such as preventing strokes, and then look at the safety issues, the bleeding issues, and determine whether or not there are things that aren't important to understand in order to see whether or not the dose of Pradaxa that somebody takes is actually safe. And whether or not the company had information related to that safety that may or may not have been passed on either to the physician or to the patient.

Q. What kinds of things did you look at to come to the opinions that you're going to give to the jury today?

A. So every project I do, I always start with what I call the basic science, so I go to the published literature. So that's articles, scientific articles that are put out for other scientists and doctors to look at in something called

a journal, just a publication every month. So I start there. So what is generally known about the drug.

And then I also go to the FDA website, and I look at what the Food and Drug Administration has had to say. You can go there and pull up information that was submitted by the company as part -- a sort of summary that summarizes what the company did in order to get the drug approved.

You can also go and find the labels for the drug. I know we are going to talk a little bit more about that, but the label is essentially the information that the physician is provided with. There's also a specific part of the labeling that is provided to the patient, and so that can be found on the FDA website.

And then in addition to that, I would go and look at documents that were not publicly available but the company made available as part of this litigation process. It's their internal files. So it will be e-mails. It may be -- I may -- I'm also reading -- you saw clips of depositions, so I will actually read of some that deposition testimony and see what the company employees had to say about what they knew over time about their product. And that will often have documents attached to it, so I'll see what they were saying about those documents.

So I look across all of that, what the publicly available information is and the scientific literature or

the papers I can find when I do my own searches. I look at what the FDA has in their files that is publicly available. And then I also look at information that I can only get through the kinds of -- well, they call it discovery, the kinds of information provided during a case as I work on the case.

Q. Let me just ask you real briefly about two of the topics you just mentioned. One is the sworn statements or the depositions of the company employees.

Can you estimate how many of those that you've reviewed?

A. I believe there's more than a dozen in this case. There was a large number of depositions, and some people had their deposition taken more than once.

Q. And, in fact, have you read the depositions of Dr. Friedman and Ms. Kliewer who testified by videotape here yesterday?

A. Yes, I have read both of those.

Q. And you also indicated that there were internal company documents that you had access to.

How did you have access to those documents?

A. So those documents are given from the defense to the plaintiffs' attorneys in the case, the people that I'm here working with here today, like Mr. Moskow. And then I will ask them for information, I'll say, you know, based on what I want to know, and then they will provide me with

information related.

So I always give them a list of things. I'm interested in this kind of information, and I need this kind of information. And I typically do that, give that kind of list because I've worked on similar cases, and I know the kinds of things that I would expect to see that the company would have. And then sometimes there's information that is attached, like I said, to the depositions, and so that will lead to me asking another question.

Q. Was there any information that you asked for that anyone told you we're not going to look for?

A. No, not at all.

Q. Based on all of the documents that you've looked at, all of the deposition -- you know, sworn testimony, the websites, the medical literature, all of that, have you formed opinions in this case as to the safety of 75-milligram dose of Pradaxa?

A. Yes, I have.

Q. Can you give the jury a general summary of what those opinions are?

A. Sure.

So the 75-milligram dose of Pradaxa, it's my opinion that it has not actually been shown to be safe and effective based on real data collected in patients as part of the approval process. The drug was never tested in patients

with atrial fibrillation, so I don't believe it's been shown to be safe and effective based on the typical process that it has undergone.

As a result of that, it's my opinion that when people were taking the drug, these people with severe renal impairment, because that's what the drug was -- that dose was meant to be used in patients with severe renal impairment. So people like that, that were then given the drug by their doctors, those people then became guinea pigs because they were the ones who didn't -- the doctors did not actually have knowledge that those people -- that drug had not actually been tested in patients before it was being used for that reason. The process was different for this drug at that dose.

Q. Let me break that down just a little bit, if you could.

You indicated that the drug was not tested in people with severe renal impairment; is that true?

A. Yes, that's correct.

Q. Can you explain to the jury what severe renal impairment is?

They saw some video yesterday, but I think we dropped them into the deep end of the pool without explaining some of that terminology.

A. So when your kidneys aren't working properly, there is different levels of it not working properly, and doctors can

put that into a category, either severe -- severe renal impairment means the kidneys just aren't working hardly at all, to moderate impairment, to mild impairment, to normal kidney function. So the patient can be graded based upon where they fall.

And if the patient has something called severe renal impairment, where they take a measurement -- I believe I was sitting yesterday during one of the depositions, and somebody mentioned the term creatinine clearance. So that is a term, a science term or a medical term that is a test that you can do to determine what level of function you have in your kidneys, how well they are working or not.

So really low values of creatinine clearance indicate that your kidneys may be severely renally impaired or moderately impaired or mildly impaired, and the doctor needs to look at that. It's the severe renal impairment that is at issue here because those are the patients that were being prescribed the 75-milligram dose.

Q. Is creatinine clearance ever abbreviated?

A. Yes.

Q. And how is it abbreviated?

A. Typically big C, little R, big C, little L, all one together.

Q. And that's just the amount of what?

A. So you want the details or just generally?

Q. Just generally.
A. So generally it's just telling you whether or not your kidneys are working probably. Are they -- the kidneys filter things in and out of your body, and they filter drugs out. They take the drug from your bloodstream, and they move it out of your body. And so they're either filtering well or removing things well or they're not.

When they don't work well, and things don't get removed from your bloodstream, you can get things that build up in your blood that can be harmful. And that's why patients that have very severe impairment have to undergo a procedure called dialysis where they actually have to help the blood clean itself. So you'll go in, and there's a procedure done where the blood is actually cleaned by a machine in order to help you get those toxic things out of your blood.

Q. At the level of severe renal impairment, first of all, is there a number that we look at as kind of a line when someone has severe renal impairment?
A. Yes, there's a standard that is applied.
Q. And what is that?
A. That is less than 30, so a creatinine clearance value of less than 30.
Q. And once somebody has a creatinine clearance of less than 30, are their kidneys working well?
A. No, they're not.

Q. Okay. So we're talking about a drug that is working in people whose kidneys are not working?

A. Yeah. When you are giving a drug to -- when you are giving Pradaxa at 75 milligrams, you are giving it to a patient whose kidneys are not working very well at all.

Q. Is there anything about Pradaxa in particular that raises concerns about people whose kidneys aren't working well even getting the drug?

A. Yes.

Q. And what is that?

A. That is the fact that Pradaxa is a drug that is mainly removed from your blood by the actions of the kidneys. So if your kidneys aren't working, you have no way to get it out of your body, and so that's really important.

Many drugs are removed multiple ways from your body. The liver can break them down so that they're no longer active in your blood. But in this case, that doesn't happen.

What happens is the drug has to -- if it is absorbed into your blood, it has to be removed through the kidneys. So if your kidneys don't work, more and more Pradaxa builds up in your blood, and that creates an issue of too much Pradaxa in your blood. And that's dangerous because too much Pradaxa has been shown to be associated with an increased risk of bleeding.

Q. What is your concern about too much Pradaxa?
A. It's dangerous, causes too much bleeding. Or can increase your risk of bleeding.
Q. Now, Doctor, you also indicated when you were kind of giving that general discussion that the 75-milligram dose had not been tested in people whose kidneys were not working well; is that true?
A. That's correct.
Q. How, if at all, has Boehringer warned individual patients in West Virginia about that?
A. Ah, they haven't. If you go to the labeling for the drug, which for the patient would be the Medication Guide, it doesn't tell you that the drug was never tested in patients with atrial fibrillation with severe renal failure to show that it was safe and effective.
Q. You also mentioned that you get too much Pradaxa, and that's dangerous.
How does Boehringer warn patients in West Virginia about that?
A. It doesn't provide you with that specific information. It just does not.
Q. Can you tell the jury whether Boehringer properly warns both patients and doctors about who is most at risk to bleed?
A. It's my opinion that they don't provide a full -- full

list of information for patients that are at the greatest risk. They provide some pieces of information, but it's never put together in what I would consider an adequate -- we will use the word warning because it's a very specific part of the drug label, and I know we're going to talk about that.

But it's my opinion that the warning that is given to doctors as well as to patients is not enough in order for the doctor or the patient to understand the real risks or the real dangers of the drug.

Q. Do you have an opinion as to whether Boehringer properly instructs doctors and patients on how to avoid or at least lessen, minimize the bleeding risks with Pradaxa?

A. They don't, and that's really important.

Q. Why is that?

A. Because there is a way that is available that the company is aware of in order to identify those people that would be a greatest risk of experiencing the dangers or the increased risk of bleeding. And that's a -- a very simple tool of measuring the amount of the drug that is in the blood.

Q. We'll talk more about that today?

A. Yes.

Q. Okay. Let me ask you kind of this formalistic thing that we need to do in court.

Are all of the opinions you've just told the jury held to a reasonable degree of scientific and regulatory certainty?

A. Yes.

Q. What does that mean to you?

A. That means that, in my opinion, it's more likely than not that I feel comfortable, I believe the evidence says that these things are more likely to happen than not.

Q. All right. Now that we've kind of got that introduction out, I want to go into a little bit more detail on everything you just told the jury. Okay?

A. Okay.

Q. So let's start with your education.

Where did you go to school?

A. So my undergraduate degree is from the University of Georgia, and my doctorate degree is from the College of Pharmacy at the University of Georgia.

Q. Okay. Let's start with your undergraduate degree.

What is that in?

A. So it's in zoology.

Q. What is zoology?

A. It's the study of -- essentially the study of living organisms, and it's looking at the differences among the different organisms such as -- I studied everything from a worm or a fruit fly up to an animal. You don't -- and even

into humans.

Q. And so you got a four-year degree in that?

A. Yes, I did.

Q. Okay. And then what did you do after you got that four-year degree?

A. I realized after I completed my degree that I was interested in research, interested in working in a laboratory, for example, and I was really interested in going into teaching at a medical school or some other type of college. So I decided to get a degree that applied, ah, sort of a science to humans. I was interested in understanding human diseases.

I didn't want to go to medical school, so what I did is I applied for the pharmacology program at Georgia. And I was lucky enough to actually get a full assistantship and a full ride, which is why I stayed there.

Q. When you were at the University of Georgia getting your Ph.D. in pharmacology, was there a particular focus or a concentration that you had?

A. Yes. So when I joined the department, there were professors that worked in all different areas of pharmacology and essentially all different types of drugs. You could specialize in drugs that are used to treat diseases of the heart, disease of the brain. A variety of cancer was another area.

I was very interested in the heart, in the cardio -- what we call it the cardiovascular system. So I was interested in drugs that are used to treat things like high blood pressure, arrhythmias, atrial fibrillation we're going to talk about today. So I specialized in an area called cardiovascular pharmacology, which essentially is just the study of drugs that are used to treat diseases that deal with the heart and the blood vessels.

Q. As part of your Ph.D., did you have to write like a scientific paper?

A. Yeah. Well, I had to write several.

Q. Can you give us some examples, then, of the kinds of papers that you wrote, then?

A. Sure.

So the program I was under, everybody had to do original research, so things in the lab that were new. And you had to write up a thick volume they called a dissertation. And then from that, my professor required you to take pieces of your work and publish it in these journals or the scientific literature that I talked about looking at.

So I published -- I worked on a drug, and within that drug I published several papers that dealt with how the drug was triggering life-threatening arrhythmias, so changes in the heartbeat, and how that could lead to death.

So I was looking at the issue of overdosage of this

drug. Too much of this drug could lead to the patient not just being treated -- and the disease was congestive heart failure I was looking at. And I was looking at how that drug got -- if the concentrations in blood get too high, you can actually trigger an event that can kill you. Essentially it was called ventricular fibrillation.

We're talking about atrial fibrillation. So I know Dr. Friedman -- I heard him say the atrium and ventricle, and he explained the difference. So I was looking at an arrhythmia that arises in the lower chambers of the heart, not an arrhythmia that is arising in the atrium or the upper chamber.

Q. Now, I hope I'm not embarrassing you.

That was approximately 34 years ago that you did that?

A. Actually it doesn't embarrass me. I'm proud of the fact that I'm still here after all that time.

Q. In addition to the papers that you published as part of your Ph.D., have you published anything since then?

A. Sure.

Q. Can you estimate the number of things that you've published in the medical literature?

A. I have about 35 or 36 papers that have been published in the scientific literature over the years. Most of my publications occurred when I was still working in the lab. But even today I still try to take the work I do and apply

it into a publication.
Q. Have you ever published about Pradaxa?
A. No.
Q. As part of your work on this project, did you ever contemplate publishing about Pradaxa?
A. Ah, I have thought about it. But there are some things that limit what I could say and do based upon some of the information and where it comes from.
Q. Okay. Let me go back to kind of the chronology of your career.
So you graduated with your Ph.D. in 1984?
A. Yes.
Q. Can you immediately go out and start pharmacology-ing or is there something in between?
A. Well, it depends what you want to do. So as somebody who wanted to go into teaching at a medical school, it was advised that I do something called post-doctoral training.
Q. What does that mean?
A. So essentially it's additional training, additional experience that you gather in the lab where I work under a more senior scientist. And I did that. I applied for a fellowship, which is a competitive program, at the National Institutes of Health. And I went there for two years and performed research in a laboratory there in Bethesda, Maryland.

Q. Is the National Institutes of Health a governmental laboratory?
A. Yes.
Q. So it's a U.S. government laboratory that you worked at in Maryland?
A. Yes. I applied for -- essentially I had a government paycheck. Essentially it was coming through them so, yes, that's correct.
Q. How long did you do that?
A. It was a two-year program, so I was there from '84 until 1986.
Q. And then what did you do?
A. So then I was -- applied for -- I sometimes call it my first real job, although I worked on these other things as well. But I applied for a job as faculty member, as a professor at a medical school, and I was lucky enough to be offered a position at the medical school in Little Rock, the University of Arkansas for medical sciences.
Q. And how long were you a professor at the University of Arkansas?
A. A little over three years.
Q. What subjects did you teach?
A. So I taught pharmacology to medical students. The job of this department was to teach the doctors in training, ah, about how drugs work and how they can be used safely and

effectively.

Q. Did you also teach toxicology?

A. Yes, I did. Because that was -- I also had -- I was lucky enough to get two separate positions. I had a position appointment to the pharmacology department, and I had a separate position appointment to the department of toxicology.

Some schools, that's all one. But in this school, they had two separate departments, so I had an assistant professorship in each department.

Q. Okay. With regards to toxicology, you told the jury earlier that you were board certified.

How long have you been board certified?

A. Since 1993, so 25 years.

Q. In addition to being a pharmacologist and a toxicologist and a consultant who works with the FDA, do you do anything else?

A. Yes.

Q. What's that?

A. So I was -- in 1997, I moved from one company out. And I was very interested in taking inventors -- so in a research environment in a medical school, for example, people that work there, the professors may make a discovery that they want to get a patent for. So a patent is something that you apply for that allows you alone to have

the rights to sell it. Nobody else can make that exact product until your patent expires.

So many people within schools seek patents, and many universities seek patents for things that their scientists invent because it has value. They can actually -- they can actually take that and sell it to a company that will then buy it and commercialize it. So I work now helping university-based inventors move their ideas from their laboratory bench to the marketplace.

Q. Do you have a particular certification or qualification to do that?

A. Yes.

Q. What is that?

A. So in order to do this, I have to sit for the patent bar exam. The patent bar is a little different than the regular bar exam. You don't have to have a law degree, but you have to have the qualifications. So you have to show that you have some type of specialized degree like in science, which I did. You have to have shown that you have worked there for a number of years. And then essentially I had to sit and take this exam, which is the same exam that people in law school take.

And if you pass it, you get something called a registration with the U.S. Patent and Trademark Office. So I have a registration with them, which means that I can

officially sign documents for my inventors and put those in for consideration with the U.S. Patent and Trademark Office.

Q. You talked a little bit about the FDA.

Can you tell the jury how long you've worked at the FDA?

A. So I've never worked at the FDA.

Q. Has that fact, that you have never worked at the FDA, ever interfered in any way that you could identify as it relates to how you work with the FDA?

A. No. No. There are many people like myself that have never worked for the FDA, but we represent our clients, or we work with our clients on problems that are related to some regulatory or FDA process.

So certainly people do work for FDA first, and then maybe do what I do. But some people do what I do, which is just gain that experience through the work they've done over the years.

I actually took some courses at one time, and I still do that every once in a while, with an organization that lawyers that specialize in food and drug law teach. It's called the -- the organization is called FDLI, the Food and Drug Law Institute. And that's one of the ways that I gained expertise and experience with the FDA regulatory process.

Q. Okay. We're going to talk more about the FDA regulatory process in a moment, but I want to go back to your work as

consultant. Okay? So don't lose that train of thought.

You told the jury that you were a consultant for how many years?

A. Since 1989 is when I did my first consulting. So almost 30 years.

Q. So in that almost 30 years, that's after you left Little Rock?

A. Yes. I left Little Rock in late 1989.

Q. Okay. What kinds of companies or individuals have you worked for as a consultant over that 30-year period?

A. A wide variety of types of people.

The majority of my work has been on -- has been with people that have a product or an issue that is under the purview or is part of the FDA, part of the Food and Drug Administration's process. So I've worked with large drug companies before helping them with issues that come up as a part of this regulatory or the FDA interaction.

I've worked on drugs, over-the-counter drugs. I've worked on devices. I've worked on cosmetics. I've worked on supplements. I've worked on diagnostics. That is another area where you -- it's a type of test that -- a laboratory that you have to get approved by FDA.

And those companies that I've worked with have been in the past large companies like a Boehringer. Today I work mostly with smaller companies because I'm very involved

right now really with that initial commercialization with people. But I do have some larger clients as well that have to -- have an issue with complying with some part of the FDA process.

Q. In the time that you've worked with companies, either big or small, and their interactions with the FDA, have you played any role in, I guess, the material that is supplied to the FDA for approval of a drug?

A. Yes, I have.

Q. Can you explain briefly what you mean by that?

A. So at different points in time over those 30 years, I've worked with clients that are actually taking data or information that they have developed that's going to be used to support -- for example, we're talking about a new drug application here, would be used like that.

So we would actually -- I worked on teams typically in the past to do this. We would write up the scientific information that would then be submitted as part of this new drug application to FDA. I've done that also for device companies and other types of submissions as well.

I've also worked with the companies on other issues after the -- after a product has already gone to market as well.

Q. You said drug new drug application. Is that commonly abbreviated in the industry?

A. Yes.
Q. And what is that abbreviation?
A. It's called an NDA.
Q. Is the NDA an important document?
A. Yes.
Q. Why is that?
A. It is the document that contains all of the information that the company is relying upon to show that their drug is safe and effective for the use it is seeking.

So in this case, the NDA was -- that we're going to be talking about -- well, the NDA that is important here is whether or not Pradaxa was safe and effective for use to treat patients with atrial fibrillation. So this was all of the data collected from all the different sources put together in a very large submission.

Q. Is the proposed label part of the NDA?
A. Yes.
Q. Who is responsible for proposing the label for a new product?
A. The company. So in this case, Boehringer was responsible for putting together that initial label that was submitted as part of the NDA.
Q. What role, if any, have you played in proposing labeling as part of a new drug application?
A. So for some of the clients that I've worked for, I have

helped contribute sections, but I have never drafted a full label. But I have indeed -- as a pharmacologist and toxicologist, certain sections of the label are relevant to what I do, and so that is the kind of things that I've done in the past.

Q. You said they are relevant to what you do.

As an FDA consultant, is there any part of the label that is not relevant to what you do?

A. So in this issue, no, all of it is relevant. But as far as the kinds of things I was asked to do as far as helping with that issue would tend to be the issues related to data collected in either humans or animals that show that the drug is either working or to show that the drug has a toxic effect. And that's the kinds of summaries that I helped drafted that were put into some of the labeling.

Q. Okay. Now in addition to the consulting work that you've talked about and the patent work that you've done, you're here on kind of a different project, right?

A. Yes.

Q. How do you describe what you're doing here today?

A. I call it litigation support, so litigation being a lawsuit. And so I'm supporting science issues that come up on one side or the other as part of the litigation process.

Q. How long have you been doing litigation support?

A. I think my first case was in 1991.

Q. And have you worked for plaintiffs, defendants, both? Could you explain that a little bit?

A. So I've worked for both, and it depends upon the kind of cases. I work more for plaintiffs in one area, and I work for a mixture of defense and plaintiffs in other areas. It just depends. There's all kind of issues, science issues that I have dealt with in the past.

Q. Over the last 20 years, would you say you have worked more closely with plaintiffs who have issues regarding drug safety or defendants defending those claims?

A. In the area of what I call -- litigation for what I call -- I call it product liabilities. That is the idea that something has been harmful to an individual. Since about 2003, almost all of that work has been for plaintiffs.

Q. Okay. Approximately how much per year do you earn in these kinds of litigation support projects for plaintiffs lawyers and plaintiffs in general?

A. Sure. So I charge an hourly rate for the work that I do. And over the years, on average, it's been about 50 percent of my income. Some years 150 to 170, some years more, some years less.

Q. Okay. And you said it's about 50 percent of your income.

How much of your time is spent doing this kind of litigation support?

A. Well, an average would be about 30 percent of my time. Some months like this month it's been a lot more. It just depends on what kind of the mix -- I have three practice areas that I do, and it depends on the mix at that particular time. There has been a lot of litigation the last couple of months.

Q. Okay. How much per hour do you get for testifying?

A. $300 an hour.

Q. And you've indicated to the jury that you've been working on this Pradaxa project, correct?

A. Yes.

Q. Approximately how long have you been working on the Pradaxa project?

A. I think I first started about six years ago.

Q. And can you estimate the total amount that you've earned over that six years working on Pradaxa?

A. The last time I looked, it was about $135,000.

Q. Now, you also said that you've testified -- you called them product liability or drug liability matters?

A. That's what I would call this but, yes, that's correct.

Q. Okay. And have you testified in courts like this one about those issues?

A. Yes.

Q. Can you estimate how many times you've done that?

A. In a trial or a deposition or both or --

Q. How about just trial, like sitting here with jurors like today?

A. Dozens of times at trial. I want to say maybe as many as 50. I don't have an exact number.

Q. Okay. And have you testified as a fact witness, somebody who was part of the company in doing the work or as an expert like you're here today?

A. My work has been as an expert. I've never worked for a drug company, for example, so my work has -- with drugs has always been as an expert.

Q. Okay. And in these, you know, several dozen, maybe as many as 50 times that you've testified as an expert, what kinds of issues generally have you talked about?

A. So kind of what I'm doing today. Regulatory matters. Understanding what a company -- what is the process that a company is under in order to get a drug approved, for example, the different things they have to do, the kinds of studies.

But as a pharmacologist and a toxicologist, I look at that data on the issue often of something called risk assessment. That is the idea of determining do the risks outweigh the benefits for a product. What are the benefits and what are the risks, and how do we look at those?

I also often, because of my background, am asked to talk about the mechanism of action of a drug.

Q. What does that mean?
A. So sitting here and telling -- explaining what it is the drug is supposed to do and how it does it, if we know. Sometimes we don't know. But if we do, it gives context for a jury or for the lawyer in understanding the information that will go through this part of the regulatory submission, for example the NDA.
Q. And from time to time as part of that work, are you asked to talk about whether or not a label adequately warns, appropriately warns?
A. Yes.
Q. Without giving us an exhaustive list, can you identify a couple of things that you might have talked about?
A. Sure. So some of the drugs that people recognize, a drug called Vioxx that was used for arthritis treatment in the past, that caused -- was shown to cause heart attacks and actually was taken off the market.

A drug called Risperdal is another one that people have heard of a lot. It's been in the news. It's a drug used to treat mental disorders like schizophrenia and bipolar, but it is also used in children to treat attention deficit disorder, hyperactivity. And that drug has -- I was testifying about the need to add a warning to the drug. It wasn't adequately warning about some of the side effects.
Q. Now you mentioned Vioxx, and you said it was removed

from the market.
A. Yes.
Q. When, if ever, had the FDA approved that drug?
A. It had approved that drug. It was approved -- I don't know the year. It was in the early 2000s, and it came off the market, I believe, in '06.
Q. And you also indicated with regard to Risperdal, you advocated a change in the warning?
A. Yes. It was actually two different -- two different types of issues have come up. But, yes, different information became available over time that doctors needed to know about. And it was my opinion that this information was something that was known and should have been put into the label.
Q. Okay. Has it been put into the label now?
A. The information -- yes. I mean, it wasn't because I caused it to happen obviously, but certainly yes. Those things that I was testifying about are things that actually have changed in the labeling for that drug.
Q. Was Risperdal approved without the warnings that you identified were necessary?
A. Yes. Originally it was, yes.
Q. I want to switch gears a little bit and talk about the FDA, if we can. I think a lot of people hear the words FDA, and you can maybe explain what means. All right?

A. Sure.
Q. Food and Drug Administration?
A. Yes.
Q. Approximately how many drugs are they dealing with on a daily, weekly, monthly, yearly basis?
A. So just in the area of prescription drugs, it's thousands of drugs that the agency is responsible for oversight. And oversight meaning from the time the applications are first put in up through the entire time the drug is on the market, the FDA has responsibilities. So there is thousands of drug products out there on the market that they are responsible for.
Q. And does the FDA have a certain -- I don't want to call it a mission, but kind of a rule or, I don't know, a standard that they apply when they are looking at drugs?
A. Yes.
Q. And what would that be?
A. So the role of the FDA is protecting public health. So when they are looking at approval of the drug, the issue is the data has to show that the risks of the drug are not out -- don't outweigh the benefits. In other words, the drug has to be safe and effective, and the effectiveness has to justify the risks that the patient is put under by taking that drug.
Q. So risks don't outweigh benefits.

Is it just a scale? They put the risk on one side, and the benefits on the other, and they say, oh, we're good?

A. Not exactly, no. But, I mean, there is -- there is -- you know, there is a -- you could use that, but that is really not what happens. It's much more -- it's more complex than just more -- more benefits than there are risks.

Q. Okay. Are they looking at how the benefits outweigh the risks in individual patients, or are they looking at how the risks and benefits work in an entire population?

A. Their decisions are based on populations. So they look at data collected in a population, and it's what that data says about the population, and that's how they will justify that decision.

Q. Is that important when you're talking about drug safety whether you are looking at the population as a whole or individual patients?

A. Yes.

Q. Why?

A. It's because for any drug that is studied, and for the data that is developed that FDA looks at, that data may not be representative of the real people that eventually are going to take the drug. It's understood that that is what happens. So this is why the FDA process includes a need to monitor or -- or look at the safety of the drugs after

they're marketed.

That's why companies don't just submit the application and walk away and say we're done. They submit the application, and then they're required to continually monitor or look at whether or not, once it's released into the general public -- and those people may not be exactly like the population that was studied initially -- that the drug still is safe and effective as it's used -- as it is intended to be used.

So they look at it in a population of atrial fibrillation patients. That's how this drug was assessed.

Q. Now you testified a little bit earlier that the 75-milligram dose was not tested before it was sold, right?

A. Yes, that's correct.

Q. All right. So how -- and I may be jumping ahead of us a little bit, but why wasn't the 75-milligram dose tested in people with severe renal impairment or severe kidney problems?

A. Because the company was looking at a different dose rather than 75, not the 75 dose. So they collected data on two other doses of the drug, but not that one. And after the process was completed, when they looked at this issue of severe renal impairment, there was an understanding that there was a need to say something about what to do for those type of people. And so the FDA actually was the one who

made the decision that a 75-milligram dose needed to be available.

Q. Okay. And we're going talk more about that in a moment.

I want to go back to why people with severe kidney problems weren't studied. Do you know?

A. Yes.

Q. Can you explain that to the jury?

A. So it's -- I call it ethics, medical ethics. It's the idea that we know we have a drug that is mostly eliminated from the body by the kidneys. So we know that people who have low kidney function are going to be really at risk if they take this drug. So as a result, in order to make the clinical studies, the studies that are done before the drug is approved as safe as we can for the patients, we excluded those people, and we said you have to have some level of kidney function in order to enter that trial.

And so they had a set number of 30 that they wanted people to be above. And that's why they were excluded intentionally because of this issue of understanding a safety issue that could be there.

Q. Can you tell the jury are you criticizing or complaining in any way that they excluded people with bad kidneys from the study?

A. No, I'm not. That was totally appropriate.

Q. So what are you saying about that? What should the

company have done?

A. So once -- well, there is a lot of other information that is --

Q. We're going to get there.

A. Yeah.

But essentially, based on what was known about the drug at the -- before the studies were even started and additionally afterwards, when you realize that you have this issue of severe renal function impacting the safety, it's my opinion that you would have a responsibility to go ahead and look at at least some people in a study that was controlled to understand what -- how those patients were going to respond for safety and efficacy. And so that is what was not done.

Instead what was done is they used a -- a tool called modeling, so -- and we'll talk a little bit about it possibly. But essentially they used an indirect way to look at whether the drug would lead to blood levels of a certain level, and that's how they quantified and determined if the drug could be safe.

Q. And you just used the term a tool called modeling.

Another way of saying it is that they used a computer program to predict what would happen in people that they didn't test?

A. Yes, that's what they did.

Q. Okay. So they never used the drug in real people, the 75-milligram dose?

A. In a clinical study, that's correct. Like they did for the other doses, that's correct.

Q. What, if any, opinions do you have as to whether that information should have been communicated to patients here in West Virginia?

A. I think it was important -- I have an opinion that that's what should have happened.

If they were going to provide a drug like this with the safety issues without letting them know that, oh, by the way, this has never been shown in a clinical study to be safe and effective in patients with severe renal impairment, then that's an issue that the doctor and the patient can discuss on whether you want to be able to take this drug or not.

Q. Going back to the FDA for a moment, you said that, you know, they have this process where they evaluate whether the risks don't outweigh the benefits, right?

A. Yes.

Q. Is that something that they kind of put together on the fly, or are those rules and regulations that everybody plays by?

A. It's -- it's a rule and a standard that everybody is aware of, and everybody has to meet that type of a standard.

And each drug is different. Some drugs, there's life-threatening risk issues. Some drugs, the risk issues you're dealing with are not life-threatening.

Q. Are there specific federal regulations that you deal with as an FDA consultant that speak to how the FDA evaluates whether the risks don't outweigh the benefits?

A. Yes.

Q. And what is that?

A. So there is something called the Code of Federal Regulations, the CFR. The FDA has a specific section, and it has the No. 21. So the 21 CFR. It's kind of a book, or you can actually go online and find them. And it lists in it in certain sections that deal with prescription drugs all of the rules and procedures that are required. It tells the company exactly what, for example, has to go into an NDA. It tells the company exactly how a label is put together. It tells the company exactly what they have to do, once the drug is approved in order -- after it's marketed, to continue to know that the drug remains safe and effective.

Q. Are those rules that you work with every day?

A. Yes.

Q. And did you use your understanding and experience of working with those rules in reaching your opinion in this case?

A. Yes.

Q. Can you explain to the jury about all of the testing that the FDA does in people before it approves a drug?
A. So it is not involved in clinical testing of drugs that are being commercialized this way. It doesn't do the testing. The company does all of the testing.
Q. I want to stop there.
So when the FDA approves a drug, what information does it have to approve a drug on?
A. All -- the information based on studies that the company, in this case Boehringer, performed. So they have -- the regulations set out these are the kinds of studies you need to do, and then the company does those studies. And then those studies are analyzed and put into this big package, and the FDA then reviews the data that has been collected by the company.
Q. Okay. So to be fair, when the FDA is reviewing the data that the company came up with, does it take it at face value or does it, you know, put it into a computer and see if the numbers actually add up?
A. It will do some of their own analysis. They have a group, it's a specialty called statistics, where people -- that is what they do. They take large sets of data like this, and they look to make sure that, ah, they agree essentially with the analysis the company has done.
So the company sends in the data, analyzes it, describes

it, and then the FDA checks that.
Q. Okay. You told the jury a little bit earlier that the FDA actually asked for 75-milligram dose, right?
A. Yes.
Q. What, if any, testing did the FDA do with regard to the 75-milligram dose?
A. They did no testing. Again, the only thing that was done, both the company and the FDA did this computer modeling.
Q. And what information did they use to put into the computer to figure out whether the 75-milligram dose would be better in terms of benefits than the risks that were involved in it in people with bad kidneys?
A. So they took data that had been collected as part of the NDA at a higher dose, 150 milligrams. That's what the FDA did. Then they took this data from a study that was done early on. It wasn't done in AFib patients, but it was done in people. And those people were given the 150-milligram dose one time, and their blood was taken, and they looked for the level of the drug in the blood.

And that information was used to put into this computer program because they had people in the study that had all different levels of kidney function. So I think there were maybe 11 people that had -- in the study that had severe renal impairment. There were, I think, nine or ten in each

of the other levels. They had some normals.

So it was a study that was called a Phase 1 study, and that's what FDA did. They took that data, they looked at the blood levels that were achieved, and they compared that information to the information that was available from the much larger -- I think it was mentioned -- RE-LY trial. So they looked at blood levels that were -- numbers from the drug in that trial to see how it changed. How did the people exposed to 150 with severe renal impairment look different on blood levels compared to the people that had normal kidney function.

Q. You gave us a lot of information. I want to break that down, if we can.

A. Sure.

Q. You said the study that the FDA used to put into the computer to figure out whether the 75-milligram dose would be safe and effective was based on giving 11 people with severe kidney problems one dose?

A. Yes.

Q. Can you tell the jury for people on AFib, do they take one dose?

A. No.

Q. How many doses would you expect somebody on AFib would get?

A. So they usually will take it for the rest of their life.

So most of the -- for example, the big clinical study done in RE-LY went on for several years. And so you would typically in development do a study for a drug that was used in AFib for several years, not just for a single dose.

Q. I think what we'll do is we'll start looking at some documents. Okay?

A. Okay.

Q. Could you turn in your book to Exhibit 143?

A. Is it in the back of the book or do you know?

Oh, I see. I've got it.

Q. Do you recognize Exhibit 143?

A. Yes.

Q. And without giving us too much detail, what is it?

A. It's a letter from the FDA that tells Boehringer their drug has been approved, Pradaxa has been approved.

MR. MOSKOW: Your Honor, I move Exhibit 143 as the full exhibit.

THE COURT: Any objection?

MS. JONES: No objection.

THE COURT: It's admitted, and you may publish it.

MR. MOSKOW: Thank you, Your Honor.

(PLAINTIFFS' EXHIBIT 143 ADMITTED INTO EVIDENCE.)

MR. MOSKOW: All right. So let's set the stage.

Q. We're in October 19 of 2010?

A. Yes.

Q. How long as of October 19, 2010, based on your review of the documents, had the 75-milligram dose been under discussion for use in people with bad kidneys?
A. I want to say only weeks at this point in time.
Q. I'm sorry. Could you repeat that?
A. Weeks.
Q. And how long had Pradaxa as a whole been under investigation as of this time?
A. Years.
Q. More than a decade?
A. Yes.
Q. We're going to look at this in a little bit more detail, but can you just tell the jury whether it is common or unusual for a dose of a drug to be approved by the FDA after only weeks of discussions?
A. I find -- in my experience, that is highly unusual. Especially for a drug like this, which was a new type of drug within -- within a class and a new mechanism of action. So a different type of drug altogether, so one that the FDA didn't have a lot of experience with.
Q. And at the time, at this time in October 2010, how long had the FDA been reviewing this new drug application, this NDA?
A. So it was something that was under a fast review process, so I believe overall maybe ten months.

But they had received information over time, so --

Q. And you said they'd been reviewing it approximately ten months.

Are we talking about, you know, a binder like the one that you and I have in front of us or are we talking about more information than this?

A. A whole lot more information than that. I mean, that would be expected, absolutely. You need to have a whole lot more than one binder.

Q. All right. For those of us who aren't involved in the pharmaceutical industry or the new drug application, are you able to give the jury a sense in terms of paper how much information we're talking about?

A. So when I first started working in this area, people had to submit everything in paper to the FDA. Now we do it -- they can do it electronically, so it's a little easier. But it used to be a truckload or more of documents, millions and millions of pages of information. Because it's everything that the company has done over the decade from their studies in cells and tissues, in animals as well as the data that they have collected in humans.

Q. And just to capture something you just said there.

When the company is developing a new drug, they will look at the molecule or the material itself like in a test tube?

A. Yes. They have to understand what is called the chemistry. So, yeah, they have to understand what it is, they have to understand how to make it, and they have to understand then what it does.

Q. They test it in animals?

A. Yes. That's what you do because it would be -- would be unethical again to go right to humans. You start with an animal in order to protect humans.

Q. And then when you start testing in humans, do you go right to sick people?

A. No. You start out in healthy people or healthier people to start with. Because, again, it would be unethical to go right to a patient, a fragile patient, somebody who had an underlying medical condition until you knew something about the dose of the drug can be safe in people generally. And then once you do that, then you move into patients with the disease or the condition that you're trying to treat.

Q. Okay. And what we're here about today, that would be people with AFib?

A. Yes.

Q. And so what is that called, a Phase 3 or a pivotal trial?

A. So there is -- that's the study -- the Phase 3 study is the ultimate study done in AFib patients that FDA relies upon to provide the kind of the defining data or most

important data that it weighs for safety, for risks and benefits. There are some studies done before that that will be in patients with AFib, but the majority -- the most important data is going to be that what I call Phase 3 study.

Q. So when we talk about the RE-LY trial, is it sometimes called a pivotal trial?

A. Yes.

Q. And it's the pivotal trial because why?

A. Because it's the one that is the largest and has the most information relevant to the patients that are going to be getting the drug. So it's large, and it has those patients specifically. And it's designed to really look at safety and effectiveness, risks and benefits, in the people that are then going to get the drug once it's approved.

Q. Okay. And so when did Boehringer specifically study the safety and effectiveness of the 75-milligram dose in people with AFib and bad kidneys?

A. They did not do that before the drug was approved.

Q. What data, what information was there as of October 19, 2010, to support the approval of the 75-milligram dose?

A. There was data on other doses.

Q. What about the 75-milligram dose?

A. There was no data collected on the 75-milligram dose.

Q. I think you already told us that's unusual.

Why is that unusual?

A. Because -- well, I think it's unusual for a drug like this. And that's because we know -- I talked about the fact that the dose you give that give you the effect you want, but it also can lead to a very serious life-threatening bleeding event. So there is not a lot of room for error when you are deciding is that dose safe and effective?

And so that's what is unusual to me with a drug like this, where the right dose, choosing the right dose is so important so that you get benefits, but at the same time you don't have too much risk.

MR. MOSKOW: Let's look a little bit more at the letter, if we could.

Going down, you'll see that there is a paragraph that says we acknowledge receipt -- I'm sorry.

No, could you just do the paragraph before it. Thank you. That's on me.

Q. Do you see that there's a paragraph -- no, just below that one -- the paragraph that says we acknowledge receipt of lots of information?

A. Yes.

Q. Is that common or uncommon that the new drug application has a lot of supplements?

A. It's common, especially for a drug like this, that I told you had a fast review process. Because they do do

submissions -- they do submissions not always all at once, but over a period of time.

Q. Okay. Is this process a one-way street? Is the company just throwing paper at the FDA or is there some sort of interaction?

A. There's interactions.

Q. So are some of these submissions responses to FDA questions or concerns?

A. Yes.

MR. MOSKOW: Next paragraph, please. Thank you.

Q. So this is the part that the company was waiting for when they got this letter, right?

A. Yes. This tells them it's approved.

Q. Okay. And everybody is going to have to bear with me. This is the first time I've used this machine.

But that is that line right there?

A. Yes.

Q. Okay. And what does that mean? I know we all assume approve means you can just go out and sell it, but what does it mean at the FDA?

A. It means that the FDA has completed its review, and it has found that the drug in their opinion is safe and effective for use as labeled. So, in other words, there is specific conditions -- it's approved -- it's not just approved for use in anybody, but it's approved for use in

specific doses in specific types of patients, and it has to be used according to the label.

Q. And then as part of the approval, they say: For use as recommended in the enclosed agreed upon labeling text.

Do you see that?

A. Yes.

Q. I want to break that down, if we can.

For use as recommended, so what was Pradaxa being recommended for?

A. Use in atrial fibrillation patients as an anticoagulant.

Q. Okay.

A. So a blood thinner.

Q. A blood thinner for people with that irregular heartbeat?

A. That's correct.

Q. All right. And then it says: Enclosed agreed upon labeling text.

Do you see that?

A. Yes.

Q. Try that again. There we go.

And is that important information for the jury in your opinion?

A. Yes.

Q. Why?

A. Because you need to understand what happens when the

company submits the label, and the process that goes on to arrive at what actually the doctor sees or the patient sees in the Medication Guide.

Q. Okay. And what is the process that gets to an agreed upon labeling test?

A. I called it a negotiation, and I think actually Ms. Kliewer also called it that.

So it's a back and forth. So the company submits with their NDA their first suggestion, this is the label we would like to use with the product. And then the FDA comes back with comments. And then there is a process -- in this case, there was -- where FDA came back. The company makes another suggestion what I'd like to see or answers a question with new information. So it goes back and forth.

And eventually before the drug can get this approval letter, there has to be an agreement on what that labeling will say between the company and the FDA.

Q. Okay. And was that done here?

A. Yes.

Q. Okay. Are there --

THE COURT: Would this be a good point to take a brief break?

MR. MOSKOW: If I could have three minutes, Your Honor?

THE COURT: Go ahead. I'll let you decide.

MR. MOSKOW: I'll be done with the document then.

Q. And let me ask you just very quickly with regard to that back and forth.

Does it end once the drug is approved?

A. No.

Q. Can we turn to the second page of Exhibit 143?

A. Yes.

Q. And do you see there's a section that says Reporting Requirements?

A. Yes.

Q. Can you just briefly explain to the jury what that means?

A. This is -- this is that section of the 21 CFR regulation. It cites something here, 314.80, 314.81.

It just means that the company is required after the drug is approved to do certain things. And those certain things means that the drug -- that the company has to continue to look at the drug after it is released into the marketplace, track whether or not there is some new safety issue or new risks they need to worry about. Or whether there is uses that appear to now be not safe, although they appeared to be safe when the drug was first tested. So those kinds of things have to be monitored or looked at by the company after the drug is released, and they have to report certain information back to the FDA.

Q. Okay.
A. And that could lead to actually a change in the label even, and so sometimes there is new labeling negotiations that go on after the drug is approved.
Q. And we'll talk about this more after the break, but my last couple of questions involve the paragraph at the top of the page.
Does the obligation that a company has to warn about the safety of the drug stop when it's approved?
A. No.
Q. When does that stop?
A. It never stops as long as the drug is on the market.
Q. Okay. And as part of that process, do drug companies sometimes communicate directly with doctors and nurses and people who treat patients?
A. Yes.
Q. Can you explain to the jury what we're talking about here with this letters to health care professional that is written at the top?
A. So a company always has the opportunity, if they would like, to convey especially important new safety information to physicians directly, physicians, pharmacists, other health care providers. It can go to a large health maintenance -- HMO. It could be distributed to all of the doctors and nurses there as well.

But essentially it's -- they can send those letters out directly to the physicians to tell them about this important safety information.

Q. When, if ever, has Boehringer sent out a letter regarding the 75-milligram dose to doctors?

A. I'm not aware of one.

MR. MOSKOW: This is a good place to stop, Your Honor.

THE COURT: All right. Ladies and Gentlemen, we'll take a 10-minute recess. You may retire to the jury room.

Dr. Plunkett, you may step down. Don't discuss your testimony with anyone.

We'll take a 10-minute recess.

MR. MOSKOW: Thank you, Your Honor.

(Recess taken from 10:32 to 10:43 a.m.)

(Jury not present.)

THE COURT: All right. Are we ready to resume?

MR. MOSKOW: We are, Your Honor.

THE COURT: Let's bring the jury in.

(Jury present.)

THE COURT: All right. Be seated.

Dr. Plunkett, you can resume your examination.

MR. MOSKOW: Thank you, Your Honor.

We don't have to put the document back on the screen, but I want to talk a little bit more about this

agreed upon label language. Okay?
Q. And you told the jury before we broke that there is a negotiation. In fact, you quoted Ms. Kliewer who testified by video yesterday about that.
A. Yes.
Q. I want to find out, whose responsibility based on your education, training and experience is it to ensure that the label is complete and accurate?
A. It's the responsibility of the company, in this case Boehringer.
Q. Okay. And is that reflected in any of the documents or rules and regulations that you work with?
A. Yes.
Q. Where is that reflected?
A. Within the regulations themselves. It talks about the company putting together the label, the process and that, again, after -- the responsibility of the company after the drug is marketed to assure that the labeling remains accurate and is not false and misleading with new information that also becomes available.
Q. Now, you said it's their responsibility to ensure that it remains complete and accurate?
A. Yes.
Q. How is that done?
A. That's this monitoring, what I call post-market

oversight by the company. So even though FDA still has a role in receiving information after the drug is marketed and is a body that is out there, and they play some role in the things they do. But it's the label, still it's the company's label, and they're responsible at all times for making sure that what is there is accurate and complete information so that the drug can be used safely and effectively in patients that have the condition that the drug is approved for.

Q. And the jury heard Ms. Kliewer and Dr. Friedman talk a little bit about this yesterday, but is there a process for updating the label?

A. Yes.

Q. Can you explain to the jury how that works?

A. So once the drug is on the market, and the label is out there, is in use, if new information -- especially information that deals with patient safety. So risks, that's really important.

If information is identified by the company, they have a responsibility to notify FDA, but they also have a responsibility and they can make that label change before FDA actually approves it. So there is two ways you can do it. You can submit to FDA the information about the label change and wait before you make the change. But there are certain kinds of information that deal with this warning,

safety risk information that a company can put into a label at the same time that they're asking for the FDA to approve it. So they don't have to wait a period of time for FDA to come back.

FDA will eventually come back to them, and it may be that there is again a negotiation over what ends up. But certainly they have the ability to put that information in their label that has to do with these important risks and something that is not already in the label or something new about the way the information is described in the label.

Q. Has BI used this process to update the Pradaxa label over time?

A. Yes.

Q. And once, twice, more than that?

A. I can't give you the exact number, but certainly there is one time that it's important in this issue because it has to do with the issue of patients with renal disease.

Q. Okay. And we'll come back to that.

But it's more than just a couple of times, right?

A. Yes.

Q. Okay. And with regard to this important time because it has to do with renal disease or people with kidney problems --

A. Yes.

Q. -- what are you talking about?

A. So the company made a change to the label that told doctors they should be looking at renal function of their patients when the patients are already on the drug. So it's the idea of understanding if kidney disease changes or their renal function changes.

Maybe they used to be mildly -- mildly impaired, their kidney function was just a little bit off, and all of a sudden they get sick, and now the patient's kidney function has gone way down. So they asked doctors to monitor or look at kidney function as the patient continues to be on the drug to see if something needs to be done either to change the dose of the drug or maybe even choose a different drug for a patient.

Q. When has this process been used to update the Medication Guide -- which is the part of the label for the patient?

A. Yes.

Q. When has this process been used to update the Medication Guide to talk about the importance of how much Pradaxa you have in your blood?

A. It's not been done at all for that purpose, that I'm aware of.

Q. Is that important information?

A. Absolutely, yes.

Q. Okay. Would it help for the jury to understand a little bit more about how Pradaxa works so they would appreciate or

understand how important that is?
A. I think so. Hopefully they will think so, too.
Q. All right. So you've talked about anticoagulants, and we've heard people talking about they are blood thinners.
How would you describe it to somebody you are meeting on the street?
A. So I sometimes talk about it as being a balance. So think about a teeter-totter in a playground, it goes up and down, up and down. And one side of the teeter-totter is this issue of preventing a stroke, and the other side is bleeding. So the drug can prevent a stroke, but it can also cause a bleed. So you want that teeter-totter to be in balance where there is no real risk of -- no large risk of bleeding, but at the same time you're preventing strokes so the teeter-totter would be in balance.
That's the ideal, what you're seeking with anticoagulants. You want each patient to be in this balance where the strokes are prevented, but they're not at a large increased risk of bleed.
MR. MOSKOW: Could I ask you to step down from the box with the judge's permission?
THE COURT: You may.
MR. MOSKOW: Thank you.
Could I ask you to take that microphone.
Q. And if I could ask you to actually draw that

teeter-totter that you just described to the jury.
A. Sure.
MS. JONES: May I just sit over here?
THE COURT: Yes, you may reposition wherever you like.
MS. JONES: Thank you, sir.
THE WITNESS: Can you hear me?
(Witness drawing.)
BY MR. MOSKOW:
Q. Okay. So what are you drawing for the jury here?
A. So this is the teeter-totter in balance. You're protecting against stroke, but you haven't put the person at such a large increase that they're expected to have a major issue with bleeding. So their blood is in a state where they're getting anticoagulation, thinning to a level to prevent strokes, but you're not at a large increased risk of bleed. And that's what everybody is seeking for their patients.
Q. What happens if you get too much Pradaxa in your blood?
A. So when you get too much Pradaxa in your blood, think about it this way, is this bleeding risk is going to shoot up. So bleeding goes way up when you get too much Pradaxa. It's known. There's a relationship between the level of Pradaxa in your blood and an increase in your risk of bleed.
Q. Is that dangerous?

A. Yes, absolutely.
Q. Why?
A. Because this bleeding can kill you. We know that -- and we know the relationship.

The company studied this issue in their clinical trial, the RE-LY trial. They collected data in patients that actually showed that the level of drug in blood -- as the level of drug in blood increases, the Pradaxa increases, as it goes up, the bleeding risk goes up.

Q. Could I ask you, before you put the pen away, to put your initials and today's date, which I believe is the 4th?

Thank you. And don't go away. I'm going to ask you a couple of questions while you are here. I'm going to ask you to draw something else.

A. Sure.
Q. How would a physician and a patient know whether or not the teeter-totter is in balance or somebody is getting thrown off the high end?
A. Based on the data they have, the only way to know would be to actually measure the level of Pradaxa in their blood. That's the data they collected that showed there is a relationship. So if they measure it, they can have an understanding, the doctor, based on the data where they fall.
Q. Can you tell the jury whether or not there is

information in the label telling doctors what you just explained?

A. That's what is missing. That's one of the big issues I have with the label is they don't tell doctors how to prevent the bleeding.

And also, there's also a relationship with this blood level, with too little that is going to lead to not enough effect, not enough prevention. So there's a range of blood levels that the company identify in their data that would be useful for doctors to understand. Too much, there's words -- some people call this excessive exposure to Pradaxa, which essentially just means too much drug in their blood increases the risk of bleeding.

MR. MOSKOW: Can I get the slide too much?

Q. I'm going to put -- you just used the phrase excessive.

A. Pradaxa or dabigatran, that's the same thing.

Okay. So dabigatran is the chemical name for the active drug in the body. Pradaxa is the name of the pill you take before the active drug gets into your body.

Q. All right. So this excessive dabigatran exposure, this idea of too much Pradaxa, where is that happening on this teeter-totter?

A. It's -- the too much is happening when the blood levels increase. And so there is a -- there is data that shows when blood levels -- too much Pradaxa in your blood gets

around about 200, the units they can measure, then that is when this shoots up.

So you can measure too much Pradaxa in the blood, you know that level, and that has been -- the data shows that that was associated with two times or two -- two times or a twofold increase in your risk of bleeding.

Q. Is more Pradaxa better for preventing strokes?

A. That is the difference. That's why this teeter-totter doesn't act like a typical teeter-totter.

Q. Why?

A. Because if this was a typical teeter-totter, and you increase the level of Pradaxa -- notice I have this going down. You would think this risk is going up, but you're preventing more strokes. That's not what happens. What happens instead is like a broken teeter-totter. The stroke risk, once you get to these levels up here where you have this increased risk, you're getting no more benefit.

So there is a really -- there is a good relationship shown in the data that as the level of Pradaxa in your blood gets higher and higher, you increase your risk of bleeding, but at some point you get no more stroke prevention. So no more benefit, but much more risk, and that's what is important to understand.

Q. While you are here I'm going to ask you to explain to the jury how Pradaxa actually works in the body.

Is that all right?
A. Sure.
Q. Have you come up with a way to describe that to the jury?
A. Yes.
Q. And how do you do that?
A. So I'm going -- I'm not an artist, but I'm going to draw a person.
I'm going to talk about something called pharmacokinetics, and I'll explain that if you ask me to. And then we're also going to mention, later I think, the other part of the equation, pharmacodynamics.
Q. All right. So you're going to be drawing something for the jury for pharmacokinetics?
A. Right. This is what I want to draw now.
Q. Now we have put a slide up on the screen.
Why did you create this?
A. So because it's a big word, it can be broken down into two simple concepts, and so I think it's important for people who don't have a background in pharmacology.
So pharmacokinetics is what the body does to the drug. It is how, when you take the drug into the body -- and that's what I was going to draw to show you -- what happens to it when it gets in the body. And the body actually changes the drug in this case.

And then the other concept, pharmacodynamics, that's what the drug does to the body. So in this case, that's how the drug causes anticoagulation or the way the drug prevents clots from forming. So that is pharmacodynamics.

Q. Why don't you go ahead and -- is pharmacokinetics sometimes abbreviated as PK?

A. Yes.

Q. So why don't you draw for the jury the way you're going to explain PK.

A. Sure. This will be PK.

Again, I'm not an artist, but this is a person.

And up there on the screen there is three things written down, absorption, distribution, metabolism and elimination. Those are the three processes that go on in the human body that take this to -- the drug going in, and you get a level of -- you are going to get a level of I'm going to call it dabigatran in blood.

So this is the process that is going to take the pill out here -- that's the Pradaxa pill. It's going to take the pill, and we're going to put it into the mouth. That's how it is taken, orally. And I'm going to show you how you get from the pill here and then what happens to getting the drug in the blood, and that's these three -- well, four processes, absorption, distribution, metabolism and elimination.

Want me to go ahead?

Q. Please.

A. So we take the drug into the body. It goes into the mouth, goes down the esophagus, and that's the stomach here. The stomach connects to the intestines.

The other organs that are important, we talked about kidneys. The kidneys are over here; there are two of them in our body. We'll call this GI. Gastrointestinal, your intestines, the abbreviation we have seen, GI bleed, that's this here.

And then I'm not going to draw all the different blood vessels and things that are out here, but essentially what happens is dabigatran goes into the stomach, and it gets into the intestines, and it gets absorbed. That's the first thing. So absorption is movement -- moving -- movement into the blood.

Q. So another way of saying absorption is the pill is in the gut, and it has to get from the gut into the blood?

A. That's right.

So pretend these little dots are -- once the capsule goes in, it starts to disintegrate, and molecules of dabigatran are released. And so you get -- just pretend these little dots -- I should probably do this in a different color.

These are the ones -- this is dabigatran that passes

through -- into the stomach and in through the intestine, and then some of the dabigatran actually ends up in the blood. But that is what is different -- another important thing about this drug is the difference between the amount of this drug that gets into the intestine that never ends up in blood. So absorption for this drug is different than for most drugs we take.

Q. What do you mean?

A. So Pradaxa, the dabigatran, there is something called absorption, and it's only three to six -- let's say six or seven, somewhere in that range.

When you take that pill, and these little molecules of Pradaxa are in your stomach and your gut, only 3 to 6 percent of it ends up in your blood. The majority of the drug just goes right out through your intestines. So 93 to 97 percent of the drug never gets absorbed. It just stays outside in the intestines and is passing through your body.

Only 3 to 6 to 7 percent of it -- and we'll just use six, because I'm going to do some math in a minute, just pretend three to six. That's how much actually -- that's why I put very few dots out here in your body and a lot of dots in your intestines that actually comes out through the body.

Q. Is it common or uncommon for drugs that are marketed in the United States to have only 3 to 6 percent absorbed?

A. In my experience, that is something that could actually stop development of the drug. It's very, very low. Most drugs are absorbed -- in fact, most of the other drugs like this drug that are used as anticoagulants are absorbed in much higher amounts.

Warfarin is almost all absorbed. Almost all of the warfarin you take in gets absorbed into your bloodstream. Other competitor drugs have absorption levels that range from 60 percent up to 90 percent, so most of it goes in versus most of it not going in. So dabigatran is unusual.

Q. What concerns, if any, do you have for the fact that 93 to 96 or 97 percent is remaining in the gut?

A. So that's another important thing about this drug. I want to skip down. Distribution, by the way, is just moving around the body.

The next part is the metabolism part. That is important for this drug, and that is because this drug is administered as something called a pro-drug. And I think somebody used the words on the videos. Instead of just dabigatran, they used dabigatran extelate. I think it is spelled that way.

So the chemical that is actually in the pill here is dabigatran etexilate. It's the pro-drug. All that means is in order for this drug to absorb into the body and be active to do what it's supposed to do, it has to be changed, and it has to get rid of this, and you have to have just

dabigatran.

So dabigatran is the active drug. Dabigatran etexilate is not active. So it has no activity on its own, but it has to be there in order to get it in.

The company found out that this drug of dabigatran, no absorption. So in order to get it in so they could give this drug and have it have an effect in somebody -- they didn't want to give it directly into the bloodstream, they wanted it to be oral, so they had to protect the drug so that it could be passed acrost into the blood. And they did that by doing something called formulation, which just means making it into a molecule that can actually pass from the gut, the stomach into the bloodstream.

But once it's into the bloodstream, it gets activated. The metabolism up there that I mentioned from the pro-drug to this, that actually happens once it's in the blood. But that also happens -- we're going to make that red. This is going to be the activated drug.

Okay. So dabigatran is red. Dabigatran etexilate is black. What happens when it gets in the gut, you actually -- all of these black dots, 80 percent of them become red dots because, in addition to being metabolized in the body to make active drug, you can metabolize the drug in the gut to make active drug.

So when you're screening this out through your gut, this

stuff that went in, it's not inactive. Actually a lot of it is active. So you have active anticoagulant in the gut, and you also have a much, much lower level of active anticoagulant in the blood.

Q. And you also mentioned that there is something called elimination.

How does that work here?

A. So elimination for this drug, 80 percent of what gets absorbed goes out through the kidneys. So to go out through the kidneys, you have to get into the bloodstream. That's that issue of -- you know, I was mentioning the filtering system of the blood that the kidneys do. So of the 3 to 6 percent that goes in, 80 percent of that goes out through the kidneys, and that's why kidney function is so important for that.

Q. Is that good for now?

A. Yeah.

Q. You can sit down for a second and then -- thank you.

A. You're going to ask me probably.

Q. Thank you. I'll have you come back in a few moments.

All right?

A. Sure.

Q. Now, Doctor, you indicated that only 3 to 6 or 3 to 7 percent of this drug actually gets absorbed.

A. Yes.

Q. Is that important information for the jury?
A. Yes, it is.
Q. Given all of the testimony that you've given, where do you rank that in terms of what they need to understand about this drug?
A. That is pretty high up there in importance because it has a big effect on blood levels. In other words, that issue of so little absorption has a big effect on what happens when you do absorb it.
Q. So you're concerned that 3 to 7 percent --
MR. MOSKOW: All right. It's over here, sorry. I apologize. They usually don't trust me with the equipment, so I'm very excited.
Q. So 3 to 7 percent gets absorbed?
A. Yes.
Q. So that means 93 to 97 percent in the gut?
A. Yes.
Q. You already told the jury that that is unusual for a marketed drug in the United States.
A. Yes.
Q. Okay. Is there a concern that you have about -- as a pharmacologist and toxicologist about the 3 to 7 percent that is actually absorbed?
A. Yes.
Q. Why is that?

A. So the best way to do it is let's compare a drug that is absorbed -- let's do three to six because I'm going to just do -- I'm doubling the absorption.

Q. Okay.

A. So if you have a drug that goes from 3 to 6 percent absorption, and that is typical, that is an average person, if you're the person that absorbs it at 3 percent, and I'm the person that absorbs it at 6 percent, that means you can double -- I can have twice as much drug in my blood just by the dose you gave.

So if you have 100 -- let's say you have 100 units of the drug, and I in my blood -- or you do because you absorb 3 percent. If I absorb 6 percent, I'm going to have 200 units in my blood. So I'm doubling the amount of drug in the blood just by going up 3 percent in that percentage of absorption.

Now, most drugs are absorbed let's say 80 percent. A lot of drugs are absorbed in the range of 80 percent. So if I go up 3 percent from 80 to 83, I'm going to make a very small change in that amount of drug in my blood. Instead of going from 100 to 200, I'm going to go from 100 to I want to guess maybe 110 or 115. So a very small change in blood for the same change in absorption, and that's what is important.

People can differ from person to person within this 3 to 6 percent range. But for other drugs, if you differ from 80

to 83 from person to person, what I get in my blood is going to be not as effective as it would be for Pradaxa.

So big issues with the pharmacokinetics, and it has big effects on blood levels, and blood levels are what drives bleeding risk. So big effect from person to person on the amount you take into your body -- just normal people. Forget the issue of kidney function right now, just talk about normal people. And then you're going to end up with people -- one person can have twice as much drug in their blood, and we know that those blood levels are related to risk.

So that -- as a pharmacologist and a toxicologist, this drug from day one has important issues that you need to worry about when you're talking about would this drug be risky in a patient.

Q. Okay. And this change from 3 percent to 6 percent, does that have a technical term in the pharmaceutical world?

A. Yes. Sometimes you will see it discussed as bioavailability.

Q. So if we use that term or the jury hears bioavailability, is an easy way of thinking about that the amount that is actually available in your body?

A. Yes. So bioavailability of the drug, if it's 3 percent, that means 3 percent of the drug ends up inside your body so it can be active.

Q. Is there a way that we talk about the difference between the people over here who absorb 3 percent and the people over here who absorb 6 percent?
A. Yes.
Q. What's that called?
A. It's called variability with people. Inter, I-N-T-E-R, variability. And I think we have a slide, but --
Q. Great.
And so that is -- let's start with No. 1, this inter-patient variability is differences between two different people?
A. Yes.
Q. Is that common or uncommon in pharmaceuticals?
A. Very common. Every drug has some level of differences between people. And let's just restrict it to blood levels to make it easier. Yeah, any drug, the blood levels that one person gets, but another person sitting next to them could be different.
Q. Okay. And then this idea of intra-patient variability, what does that mean?
A. So that is the blood level that I have today versus the blood level that I'm going to have two weeks from now. So it's the idea that I can take the same drug every day for weeks or months or years. And if I was to take the level of drug in my blood on day 1 versus day 30, that level could be

different. So that is differences just due to me, and that's due to things that happen to me.

So for example, with this drug, if kidney function changes in me day to day, that's going to lead to my variability intra-patient. If two people each have different kidney function, that's the difference between those two people, not just within that same person.

Q. All right. And as you're looking at this idea of, you know, my drug levels today may be different than my drug levels tomorrow, how do you know that?

A. You have to measure it. And in this case, we did that. They did it -- and when I say we, I didn't do it, the company did that.

They had a study where they actually -- in that clinical study we are going to talk about, RE-LY, that big Phase 3 study, they actually did a good thing. They actually measured blood levels in their patients, in thousands and thousands of people, and they were able to look at what are the differences in the same person at different times. But the main focus was looking between people. They -- even though they took multiple samples in people, the same person, the big issue was looking at what are the differences between individual patients.

Q. Okay. Now earlier you were talking to the jury about pharmacokinetics or PK, what the body does to the drug.

And that's our gingerbread man here, right?

A. Yes.

Q. We also talked a little bit about pharmacodynamics, what the drug does to the body, right?

A. Yes.

Q. And I think the jury heard the phrase trough and peak.

Are those terms that are used in pharmacodynamics or PD?

A. Yes. It's how you relate PK to pharmacodynamics. So the relationship between those two things, what the body does to the drug and what the drug does to the body, you can look at that in terms of the levels at the lowest level in the blood, which is the trough, versus the highest level in the blood, which is the peak.

Q. Okay. Do you have a way that you can draw for the jury to explain how that works with Pradaxa?

A. Yes.

MR. MOSKOW: With the Court's permission, could you come down and do that?

THE COURT: You may.

THE WITNESS: So as a pharmacologist, one of the things that I mentioned they did in this study is they collected levels of the drug in patients over time. So this is the -- this would be blood level, and I'm just going to say of a D for dabigatran, and this will be time.

BY MR. MOSKOW:

Q. And just to be clear, every time you talk about dabigatran, is that the same thing as Pradaxa?

A. Yes. It is the active form of Pradaxa, that's correct.

Q. Okay.

A. So I may use them interchangeably.

So pharmacologists want to know how much blood -- how much -- what's the level of drug in blood over time. So they do these experiments, administer the drug and monitor the patients to look for the level of drug in blood.

So let's just say you take one dose of the drug, just one pill here. Typically if you take one pill, the blood level goes up, and then your blood level goes down over time. So time is going out here.

So you take the pill, you absorb it. As absorption goes on, you get to what's called a peak level. That's the most drug that a person is going to get in their blood when they take that pill in, and then they're going to get down here where it is gone.

That is one pill, but most -- a pill like this is not taken just once. It's taken every day for weeks and weeks and months and years. So the curve looks different when you talk about multiple doses.

So now I'm going to draw a curve where I'm going to give -- that's what this arrow mean, I am giving a new dose of the drug. For this drug, you give it every 12 hours. So

this could be 12, 24 hours, 36 hours. So one dose, two doses, three doses. So I'm going to draw that first in black, and I am also going to draw it in two different patients, so I'll do two colors.

So you give the drug, it goes up, reaches a peak, and you give another one. So then instead of dropping way down, it goes up again. And instead of -- you give another one, and it never has time to go all the way down, and you build up what's call a steady state. That means the amount of drug in your blood reaches a level that is fairly steady around -- it has lows and highs every day, but it's in a range between doses.

So now I talked about peaks here, this is called a trough. That's the other word. So peak and trough, peak and trough, peak and trough. So every time you give the drug, you have a low, and you have a high that is achieved.

Q. Now is this a typical Pradaxa patient that gets to a steady state like that?

A. Yes, and it happens pretty quickly. Within a couple of days, people get to a steady state.

Q. What happens if you have somebody with bad kidneys like the people the 75-milligram dose is supposed to be used for?

A. So that is important to know the difference, and that's why I'm going to use a different color, the red being people with the kidney function.

So now we are going to draw this curve. So this curve, the people with kidney function, they are going to start here. And instead of ever really eliminating, because their kidneys aren't working, they end up with much higher peaks and even higher troughs because they can't get rid of the drug.

Especially with a drug -- this drug is given every 12 hours, but for some patients with this kind of severe kidney disease -- there's another pharmacokinetic term called half-life that we look at. And we know for the typical patient who takes Pradaxa where their kidneys work fine, half, 50 percent of the drug about, that you actually absorb, will go out in 12 hours. So the blood level should drop by about half, 50 percent out. So that's how the blood level drops.

However, for a patient with kidney problems, with kidney impairment, the kidney impaired --

Q. Severe --

A. Severe, that's true. This is severe I'm showing. That half-life more than doubles. Now we go from 12 hours to get 50 percent out to over 27. So that means if you are given a new pill at 12 hours, you still have well over half that drug that you gave before in the body. And that's why these blood levels can be higher in a patient with kidney impairment than a patient that doesn't have kidney

impairment.

Q. Thanks.

Now, Doctor, you said that the data that you were talking about for absorption and elimination and inter-patient variability and intra-patient variability and all of these things that you were just talking about, that data or that information comes from where?

A. It comes from the company, comes from Boehringer in their Phase 3 clinical trial.

Q. And that's the RE-LY study that we've heard about?

A. Yes.

Q. Maybe just before we look at some of the RE-LY study information, can you just explain to the jury what happened in RE-LY?

A. So how it was designed, is that what you're asking me, or what it was studying?

Q. Yeah, and how many people, who got what.

A. Sure. So RE-LY was a typical Phase 3 study in that it was very large. Other studies that are done early may have several dozen people or hundreds of people. This study, I think was told you they had about eighteen or 19,000 people in it, had a large -- was a very large study.

Over 6,000 people were given warfarin. Over 6,000 people were given a lower dose of Pradaxa at 110 milligrams. And then another group of about 6,000 people were given 150

milligrams of Pradaxa twice a day. So 110 twice a day or 150.

So there is two groups of people that get Pradaxa, one group of people that gets warfarin, and they're comparing the differences in whether or not the people have a stroke or they have a bleed in all three groups. But in addition to that, in the Pradaxa patients, about 9,000 overall -- so some in both of the dose groups -- they took blood levels. And they have blood level data that they were able to see how that blood level related to whether or not the person experienced a bleed or experienced a stroke.

So that is how when I'm saying too much Pradaxa increases your risk of bleeding, that is the data they collected to actually look at that. And that's really important. I actually -- it was a -- it was a good design in that they had two doses, and they had both pharmacodynamic data on prevention of stroke and whether or not people bled, but they also related that to blood levels and pharmacokinetics. And so it gave us a lot of information that is very useful in understanding how this drug can be used safely and effectively in individual people that then take it later.

Q. When was all that information collected?

A. It was collected before the drug was approved. So I think in 2009, they had finished the RE-LY study, and the

drug was approved in late 2010.
Q. And had some of that information published in 2009, 2010?
A. Yes, that's correct.
Q. And when we say published -- when I say published, what do you understand me to be talking about?
A. So I know in the video they mentioned that they had these investigators at a university in different places that performed the study. Those scientists, plus scientists from the company, put together a paper, a publication, and they submitted that to a journal, the New England Journal of Medicine, and that paper was put out for other doctors and other scientists to look at.

So we call it a peer-reviewed, P-E-E-R, publication. That just means that other scientists have judged the quality of the data before it was actually put out there for other scientists to use and rely upon.
Q. And is the peer-reviewed literature or the peer-reviewed science important?
A. Yes.
Q. Why is that?
A. Because it's what people like me or anybody else, a doctor can go to and feel it's reliable information. But he can use -- for example, if he's making a decision on what drug to use for his patient. Or me as a scientist, I can go

there and say this is reliable information that helps me understand whether or not the risks outweigh the benefits of the drug or what the drug does, how useful it was. Those are all questions you can answer by looking at that publicly available peer-reviewed information.

Q. After Pradaxa was on the market, has BI continued to analyze that data that they collected from the RE-LY trial?

A. Yes.

Q. If I could turn you in your book to Exhibit 3247.

A. Back or front?

Q. Way at the back.

A. Way in the back. Okay.

Q. I hope they are numerically in there so you can find them. If not, that's my fault.

A. I have it.

Q. Oh, great.

And do you recognize this paper?

A. Yes.

Q. What is it?

A. This is a paper published by the author -- the authors are people within Boehringer as well as these scientists who worked on the clinical study.

And they took just the data on plasma levels --

Q. Don't give me details, just --

A. I'm sorry.

So it is a published paper in the peer-reviewed literature by those individuals.

MR. MOSKOW: Your Honor, this is Exhibit 3247. Permission to publish?

THE COURT: Any objection?

MS. JONES: No objection.

THE COURT: You may proceed.

MR. MOSKOW: Thank you, Your Honor.

Q. So you indicated that Exhibit 3247 includes people from Boehringer?

A. The authors are from Boehringer, yes.

Q. Okay. In fact, the first two authors, Dr. Reilly and Dr. Lehr --

A. Yes.

Q. -- are from Boehringer?

A. That's correct.

Q. And actually so is the third, Sebastian Haertter?

A. Yes.

Q. And is that important for you as both a scientist and a regulatory person that you are evaluating this paper?

A. Yes.

Q. Why?

A. Two things.

First off, when you see a paper, whoever is listed first, the first couple authors, those tend to be the ones

that were most involved with the analysis and writing of the paper. They're called the senior authors that usually show up. Sometimes the last author is also important when you talk about academic people, people at universities. But usually the first ones are the ones that actually did the work.

And then it's also important, the second issue is because they are with the company, you need to understand that this paper was indeed something that was developed -- something the company knew about. They were involved in the analysis. So this was the company's analysis of the data that they had collected.

Q. And I think you told the jury this already, but the data came from people who are in the RE-LY trial?

A. Yes.

Q. When people are in trials, in clinical trials, is there a process where they're told what the benefits and the risks of the drug in the trial will be?

A. Yes. That was really important to my opinions about this issue of not testing. That's a really important distinction.

Q. Why? Can you explain that to the jury?

A. So if you decide to participate in a clinical trial, you undergo a process called informed consent. That means before you agree to participate, you are sat down, and

you're told here's the things that can happen to you if you're in this trial. We don't really know yet if this drug is entirely safe and effective. But if you're willing to work with us on this trial, then you're going to be helping us generate the data to prove it's safe and effective.

So informed content by people in the trials is a really important process. They're told that this drug has not yet been approved, it's not yet known to be safe and effective. But if you're willing to participate, that will help us collect the data to show that.

Q. How did that happen to people who got the 75-milligram dose once it was approved for marketing in the United States?

A. That's what did not happen. That's why I said I have the opinion that this drug was not properly tested or shown to be safe and effective. It's really important because -- that's why I made the statement about guinea pigs, because people didn't know that this drug that they were taking -- whereas these people know.

We know we are involved in a test, and the test isn't guaranteed. Whereas when a drug is approved, it's assumed that those drugs are safe and effective for use.

Q. Going back to this paper, it was published in the Journal of the American College of Cardiology; is that right?

A. Yes.
Q. And I guess I'm not telling too many tales out of school.
The American College of Cardiology is for heart doctors?
A. Yes. Cardiologists, those are doctors who treat diseases of the heart.
Q. Okay. And was this paper aimed at people who treat diseases of the heart?
A. That is how I would -- that's what I see when I see it published there.
You tend to -- as a scientist, you try to publish your paper in a journal that will impact the scientists that you want to read it. So when I have done studies, I published in a pharmacology journal because I'm interested in other people like me seeing my results.
Q. Who typically prescribes Pradaxa?
A. Typically -- well, it's prescribed by cardiologists, but it is also often prescribed by internists, more of a general medicine doctor as well. It's both kinds.
Q. Now when, if ever, have you prescribed Pradaxa?
A. Never. So I'm not a physician. I don't treat and diagnose patients. Instead what I do is I'm someone who has studied and become familiar with and have actually taught medical students about what drugs do to you, how they have the effects that you're desiring them to have.

Q. Okay. Would it be fair to say that this article having been written for doctors is kind of scientific?

A. Well, actually this one is even more scientific than some doctors can handle, I would argue. But, yeah, it is. It has a lot of details that are really dense or can be difficult for somebody who is not a -- I would argue that if you're not a pharmacokinetics person, somebody who understands how drugs, you know, get into the body and what happens, that this paper could be difficult.

Q. Okay. Can you work with me to help explain some of these concepts to the jury?

A. Sure.

Q. Let's start with the title, it's a mouthful: The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients.

What's the simplest way you can explain what they were looking at?

A. They're looking at whether -- how the level of drug in the blood relates to the risk of bleeding or the risk of stroke. So it's finding out what did the level in blood mean for people that either have a stroke or have a bleed.

Q. Okay. And when they talk about patient characteristics, what are those?

A. Those are things such as kidney function, so looking at

how the kidneys work. They also looked at how the liver works. They look at age, how old you are. They look at do you have heart disease, do you have hypertension. Those are all characteristics.

Any person that comes into the study, not everybody is exactly the same, and so they look at what is it about each of the individuals in the study, and can some of those things about you influence the level of drug in your blood? So, for example, kidney function, they look at how that affects drug in the blood.

MR. MOSKOW: Okay. If we could look at the first line of the conclusions, please, on the abstract, first page.

So this conclusion, I just want to read the first line. It says: Ischemic stroke and bleeding outcomes were correlated with dabigatran plasma concentrations.

Q. First of all, what does that mean?

A. That means what I tried -- what I think I said. As the drug -- the level of the drug in the blood goes up, you increase your risk of bleeding. And on the issue of ischemic stroke, as the level of the drug in blood goes down too far, you no longer are preventing those strokes.

So the level of drug in blood is really important to being able to predict will somebody be at risk of bleeding or will somebody be at risk of not having proper stroke

prevention.
Q. Is there a term that people in pharmaceuticals, pharmacologists like yourself, use to describe that range where somebody is getting enough for it to be effective, but not so much that it is dangerous?
A. Yes.
Q. What is that called?
A. It's sometimes called the therapeutic range.
Q. Therapeutic range.
Do some people call it the safe range?
A. It can be called the safe range if you are wanting to focus especially on the upper end issue. But on this case, it's not safe to not prevent stroke, so I would agree it's important.
Some people call it the optimal range, too. You'll see that word used, the optimal range of -- the optimal dose that produces a range that you want so the drug is safe and effective. You see that.
Q. What about target range?
A. Target range is another word that is used. It's a way -- you know, those blood levels that you want your patient to fall in or you want somebody to have in order to -- to understand that you're at the best balance you can be between preventing strokes and preventing bleeds.
Q. When the jury sees the word correlated in documents that

we're going to be looking at, what should they take away from that? What is important about that word generally used in the scientific context?

A. So correlate means things go together. So in this case that means if -- that means the blood level is related to the risk of stroke or the risk of bleed. So it means the two things predict each other.

So if you know your blood levels are too high, that's predictive of your risk of bleeding. If the blood levels are too low, that allows the doctor to have a better understanding or allows the company, actually, to have a better understanding on predicting what their risk of not preventing ischemic stroke was.

MR. MOSKOW: Okay. If we could go to page 2, Gina.

I want to pull out just a couple of things in this paper. And if there's time we will go through others, but I really want to focus on this language that starts with however.

And it says: However, there is a large variability in the plasma concentrations achieved with any given dose depending on absorption, renal function and other patient factors.

Q. How, if at all, does that language kind of line up with what you've already told the jury?

A. Well, that's a -- that's an issue of inter-individual

variability, you know, changes between people. That's what that variability is talking about.

So it lines up -- as I told you, that you could double the amount of drug in your blood if you absorbed twice as much, that is what this is talking about here. It's that general relationship between how the level of drug in your blood is affected by things like how much is absorbed, how your kidneys work, and then there's also other things they found.

Q. And they actually identified in this paper those other things as well as the kidney function, right?

A. Yes. They looked at that in their data.

Q. Okay. So let's move to page 3, please. And there's a section on the right-hand side of the page called Demographics.

Do you see that?

A. Yes.

MR. MOSKOW: It's magic. And the part I wanted to ask you about is the part that starts about four lines down on the right.

It says: Renal function, and it uses that CrCL that we talked about earlier, was a key determinant of plasma concentrations. The subjects with moderate renal impairment, between 30 and 50 milliliters per minute creatinine clearance, showed a 2.29 fold higher trough

concentration than the subjects with renal function undiminished by age, and then it says CrCL greater than or equal to 80.

Q. Could you put that in English for us?

A. So what they found was that if the kidneys didn't work properly, and people's kidneys were working where they were clearing compounds in the range of 30 to 50 mils per unit -- that's just a unit. That is people who have moderate -- not severe that we talked about earlier. These are moderately renally impaired. That if you looked at their blood levels, that the people with that level of kidney impairment were going to have at least twice as much drug in their blood at that low level, the trough.

So trough is important, and I think we may be talking about that a little bit later, but essentially just remember concentration of the drug in blood. So the Pradaxa in the blood was much higher, over two times higher in patients whose renal impairment was at the moderate level.

Q. Now are these the people with the bad kidneys who are getting the 75-milligram dose?

A. No. These were people getting either 150 or 110.

Q. So what data do we have specifically identifying how much the concentrations changed between people with good kidneys and people with bad kidneys?

A. In these AFib patients, we do not have that.

MR. MOSKOW: All right. If we could go down to the next paragraph on the page.

It reads: Concentrations of dabigatran increased with age with a 68-percent increase in trough concentrations in patients age greater than or equal to 75 years compared with those with less than 65 years. Renal function was highly correlated with age.

Let me stop there.

Q. What does that mean?

A. So the second sentence means that as you get older, your kidneys don't work as well. So we know that, we know older people's kidneys don't work as well.

They're talking about two specific age ranges, the greater than 75 and then the less than 65, because those were some of the age ranges where the people in this trial were -- were segregated. They looked for people at different kind of increments, people under 65, people over 65, people over 75.

They were older patients in the trial generally, and I believe the average age was in the 70s. But they wanted to see now, okay, we know your kidneys don't work as well as you age, what about looking at the concentrations in the blood? And they see that, as you age, indeed the concentrations increase.

Not as much as you saw related just to kidney function.

There we had -- if you were to take 2.29 times, that would be 229 percent. So we get a 68-percent increase, a smaller increase related just to age, but definitely both those things are important. Renal function is worse, but the age alone was associated with the difference.

Q. And what does that mean for somebody who is in her mid 80s, for example?

A. That means if you're in your 80s, you're even more likely to have a higher blood level of Pradaxa just because you're old, regardless of how your kidneys work.

Q. Now the last sentence is up on the screen: Concentrations in female subjects were approximately 30-percent higher than those in male subjects.

A. Yes.

Q. Does that just mean that women have more of this drug in their blood than men?

A. Yes. That means -- and some of it is related to the fact that women -- men may be bigger. The bigger you are -- we all take -- I take a 150-milligram pill. Somebody else that weighs twice me could take a 150-milligram pill. So that affects it.

But also there is often issues where women and men have different pharmacokinetics. So we know that females are going to have more drug in their blood with Pradaxa than males were in this study.

MR. MOSKOW: I now want to turn you to page 5 of the paper. And this is a pretty dense paragraph, so I'm going to stop and ask you as I'm reading what something means.

Okay?

THE WITNESS: Okay.

MR. MOSKOW: So the median trough and post-dose concentrations were 55 percent and 36 percent higher, respectively, in the subjects with a major bleeding event than those in the subjects without bleeding events.

Q. What does that mean?

A. It just means that regardless of whether you talk about the lowest level in the blood or the highest level in the blood on any given date, these people that -- the people that bled had more in their blood.

So, again, it is that relationship. Too much Pradaxa puts you at an increased risk of bleeding.

Q. I want to skip down a little bit here.

At the bottom, you see median?

A. Uh-huh.

Q. It says: Median plasma concentrations in subjects with an ischemic stroke, or SEE, were not different from those without these events.

Do you see that?

A. Yes.

Q. What does that mean?

A. That just means -- this is the other end of the curve. So that means that the plasma concentrations, when you looked at these people that did or did not have a stroke, there didn't appear to be as big a difference in what they found. So there was less relationship on the low end of the curve than there was on this issue with bleeding.

So if you're going to take blood levels of this drug, the highest, too much levels were really predictive of bleeding events. The lower levels, it's a little more difficult to say what is that absolute lowest level. When you go below that, we see no effect on prevention.

MR. MOSKOW: So I don't know -- can the jury see this from here? Do I have to move it? Great.

Q. So we're looking at the teeter-totter?

A. Yes.

Q. So what is that language telling us about this part of the curve?

A. So it's -- that's that -- it's telling us what the red line -- this is actually my broken teeter-totter, this whole paragraph. It's the idea that on my right side, where it goes up, it is shooting up, the bleeding -- yes -- that's the side where the first sentence is talking about as concentrations go up in the blood, bleeding risk goes up.

But then on the other side, which is stroke prevention, it is saying that there didn't appear to be the same type of

relationship, strong relationship between the level and the likelihood that you would have a stroke.

MR. MOSKOW: All right. I'm going a little bit more slowly than I meant to, so I'm going to take control, and I'm going to do this here. Thank you.

All right. Hopefully figure this out.

Q. If we could turn to page 3 again of the paper. Can you do that with me?

A. Sure.

Q. Do you see that there is a table at the bottom of the paper?

A. Yes.

Q. I'm going to focus in -- I want to focus in on this column here. Okay? So under the 150-milligram dose.

A. Yes.

MR. MOSKOW: I don't know if anybody can see these numbers. Let me try to make this a little bit bigger.

No, it's fine. Thank you.

All right. There we go.

Q. And I just want to walk through quickly with this so we can explain to the jury what this data means. All right?

A. Okay.

Q. So on the first thing on the left here, do you see this P10?

A. Yes.

Q. What does that mean?
A. That is a number that is identifying the level where the lowest -- if you take 100 people and line them up -- or 10 people and line them up, this would be the No. 1 patient over here, the one with the lowest levels of Pradaxa in their blood. And then P90 would be that person on the other end with the highest levels.

So we're taking the population of blood levels, and we are ranking them from lowest to highest. And we have P10, which is the patient with the lowest level in their blood, and the P90 is going to be the patient at the top with the highest level in the blood.

Now they had more than 10 patients, so these numbers are going to be an average of those people, 10 percent of the people, the lowest 10 percent, and then the highest 10 percent.

Q. So what was the level of Pradaxa in the blood of the lowest 10 percent?
A. So these are going to be those trough levels, so this should be a level that the person had in their blood before they took their next pill. Okay.

So the average was 39.8, about forty -- the units are called nanograms per mil. Just use the number 40.

Q. And then the highest 10 percent, what number were they at?

A. They were at 215.
Q. Now, were all of the people at P10 at 39.8?
A. No. So if you look down here where it says min and max --
Q. Here and here?
A. Yeah.
Q. So in this population of people just overall, someone had a level at trough as low as 1.04, essentially 1, and somebody else had a level when they took the samples as high as 809. So that is how the span of the blood levels before they took their next dose ranged within the population they studied.
Q. So in this study, there was somebody who had as much as 809 units in their system?
A. Yes. And, again, these are all people taking 150 milligrams a day, so it's -- and these are patients with AFib.
Q. And there was somebody who only had one?
A. That's correct.
Q. What is that variability called, the difference between one and nearly 800 times that?
A. So there is a number here. See the CV percent, the second line?
Q. Right here?
A. Yeah.

Q. Okay.
A. So that 81.9 is a way that you can describe the variability in blood levels in these people. That means that there could be numbers that were -- the difference between the numbers, the variability from number to number varied by 80 percent. That's a really high level of variability in a controlled clinical study. Maybe not so high when you talk about the real world. But in controlled clinical studies for most drugs, those numbers would be more like 30 to 50, not 80, and maybe even as low as 20 for some drugs.
Q. Now, as part of the work that the authors did on this, did they use, like, graphics to try to describe what we were just looking at?
A. Yes. They tried to take all the data and show it visually. Because for a doctor that didn't want to delve into necessarily all of the details, they could go to a graph and visually understand what the -- what the results showed.
Q. Okay. And I put up Figure 2 on page 6.
Do you see that?
A. Yes.
Q. Can you just generally describe for the jury what this is showing us?
A. So the red -- the area shaded in red with the red line,

that is the calculate -- they predict what was somebody's risk of experiencing a bleeding event based on their blood levels at the lowest level, the trough. And then the blue area is what is the probability that somebody is going to experience a stroke.

So obviously the lowest levels below 50, you'll notice the stroke curve is higher, and the bleed curve is lower. But as the blood levels go up and up and up, the bleed risk shoots up, but you'll notice the stroke area stays fairly constant. So, again, no more benefit at those higher blood levels. But at some point, the risk there you see is actually going much higher than the risk of stroke.

Q. Okay. And that P90 and P10 that we looked a little while ago --

A. Yes.

Q. -- is that reflected at all on here?

A. Yes. If you take that -- there's a horizontal line at the top that says DE 150 BID. That just means dabigatran etexilate, Pradaxa, at 150 milligrams given twice a day.

Q. Okay.

A. And then it draws a line, and the top -- the far left of the line, drop it down all the way to the concentration, that should be about your P10. And over here at the top of the line, drop it down, that should be identifying your P90.

Q. And based on the data in this study and what we're

looking at here, what do we know about these people in the P10?

A. So the P10 are people that aren't getting enough drug. They're at an increased risk of stroke. That's why you see that curve rising.

Q. Okay. And what about the people over here in P90, what do we know about them based on the data that you've reviewed?

A. They're getting too much. So too much Pradaxa in the P90, too little Pradaxa in the P10.

Q. What do you call this area in the --

A. The area in the middle has been identified -- actually the company, some of the scientists identified it as a therapeutic range. When I mentioned that, that is the blood levels that if you stay within that zone, between P10 and P90, you have -- you are preventing the strokes, but you haven't increased your risk of bleeding to such an extent that the risks are outweighing the benefits based on this data.

Q. Were you in the courtroom yesterday when the jury heard the questioning of Ms. Kliewer?

A. Yes.

Q. And there was the discussion about a Dr. Temple from the FDA. Do you recall that?

A. Yes.

Q. And they used a term, sweet spot.
A. Yes.
Q. Do you have an understanding of what that means?
A. Yes.
Q. What is it?
A. So it is -- the sweet spot is that range in the middle here. You can see where the lines are intersecting where you have -- you are minimizing the risk of bleeding, but you are maximizing the prevention, and so you're targeting there. You're trying to get your blood values in that range based on their data so that you have less risk of either, less risk of stroke and less risk of bleed.
Q. Now while we're looking at this figure, it looks like the stroke risk continues to go down even as the bleeding risk is going up.
That's what it looks like, right?
A. So -- you mean the blue line?
Q. Yes.
A. Yes.
Q. Is there anything in the paper that would suggest that that is not really what is happening?
A. Yes. There's a statement in the paper where the authors talk about the fact that there is really no significant increase in prevention, so no significant decrease in stroke risk, the opposite of increasing.

MR. MOSKOW: So I'm bringing your attention to page 7 and the paragraph on the bottom left.

THE WITNESS: Yes.

MR. MOSKOW: And it says: Because the risk of ischemic events is relatively constant for patients with higher plasma concentrations, including the daily -- excuse me -- reducing the daily dose to such patients may reduce the risk of bleeding without appreciable loss in efficacy.

Q. Can you put that in English for us, please?

A. That means that what is most -- if you want to talk about risk to the patients, the higher levels are what's important more than looking at the issue of prevention. So if you give more drug, you're not going to prevent more strokes, but you have a much greater risk of getting a bleed. So the weighing of risks and benefits is different when you talk about bleeds and strokes.

MR. MOSKOW: And if I bring you back to page 6, the page that had the chart that we're -- the chart we went through or the figure, I want to look just to the right of that.

You see there's a statement here that says: Compared with the median trough concentration of 88 nanograms per milliliter adjusted for age and CHADS2 score, the rate of major bleeding doubled at concentrations of 210 nanograms per milliliter.

Q. What does that mean?
A. So what they're doing here is they're saying if you look at a blood level of 88 nanograms per mil in this work that they've done, and you relate that to certain patient factors, like how old they were -- the CHADS2 score is a clinical assessment. They look at the patients and whether or not they have hypertension, diabetes. It's looking at these underlying risk factors for stroke for sure, but other cardiovascular conditions.

So when they have people, they look at their age and that kind of underlying risk factor score that they see at 88 nanograms per mil and compare it, that when you get from 88 to 210, you've doubled the risk, so 200-percent increase in the risk of bleeding in a patient like that, that has certain -- that are adjusted for age and underlying conditions.

Q. This rate of major bleeding doubled. This doubled it.

Is that important to scientists like you when you're evaluating data?

A. Yes. When you are talking about human -- human data and risk, yes, the twofold increase or the doubling is an important number.

Q. Why is that?

A. So when you analyze a data set, and you see things that are doubling, more than two times of an increase in risk, if

you were to go and analyze that data with different kinds of tests you can do, you would find that that relationship between the increase, the doubling of the risk and the blood level are more likely than not a true event, not something that is just due to chance.

In science, when I do a study, some of the results I get could just be because it happens, it's chance. But this means that when you get a doubling, you're less likely to be just something that could just happen, but indeed is more likely to be a true relationship; in other words, that the blood level is actually affecting directly that risk of bleeding.

Q. When you were giving your opinions before, and you used the phrase more likely than not, how if it all does this doubling of the risk here fit into that?

A. Oh, it absolutely is consistent with the more likely than not. Absolutely.

Q. Finally, before we move on to something else, this P90 and P10, each one of those is 10 percent of the people on the drug, right?

A. Yes.

Q. So it's 20 percent altogether or one in five?

A. Yes, that's correct.

Q. How do we know -- if you had five people here on Pradaxa, how do we know who is getting too much and who is

getting too little?
A. The only way to know is to measure it in their blood. That's what this data is.
Q. Have there been further studies looking at the data from the RE-LY trial and how it relates to the gastrointestinal tract?
A. Yes. There was another study.
Q. Okay. Do you have Exhibit 3124 in your book there?
A. Yes, I do.
Q. And can you, without giving us too much information, tell us who the authors are?
A. The senior author is John Eikelboom, and this is a paper published in 2011, I believe.
MR. MOSKOW: Your Honor --
THE WITNESS: You need the journal or is that good enough?
MR. MOSKOW: Permission to publish?
MS. JONES: No objection.
THE COURT: You may.
MR. MOSKOW: Thank you, Your Honor.
And I really want to move quickly through this, if we can.
Q. But just from the title, can you tell the jury what this was looking at?
A. So this is, again, data -- you see down low, the last

part of the title, the RE-LY trial. More data from the RE-LY trial, they are analyzing it. But in this case they're looking at -- specifically looking at bleeding risk. So they're going to look within this database, and they are going to try to parse out the people that bled and look at very specific kinds of bleeds.

So not all bleeding is the same. We have GI bleeding. We have bleeding in the brain. I think Dr. Friedman talked a little bit about the different kinds of bleeding there can be.

MR. MOSKOW: Okay. If we could jump to page 8 of this paper, please. And I want to -- it is still hard to read from far away. If we could take out the paragraph on the left, the bottom left.

Would it be any bigger if we just started it higher, please, just so the jury can see it better?

Okay. Can you start lower and make it bigger? See where it says higher bleed? Right at the beginning of the paragraph. Great. That's a little bit bigger. Thank you.

So, Doctor, this is talking about: Higher blood concentrations of dabigatran with increasing age might have contributed to the higher risk of extracranial bleeding with dabigatran compared with warfarin patients, age 75 years.

Let's stop there.

Q. So what is that telling us?

A. So it says that the more Pradaxa, dabigatran you have in the blood as patients got older, as their age went up, they were able to look at the risk of bleeding outside the brain, extracranial. So now they are focusing on these other bleeds, like the GI bleeds, other places in the body, and they see the higher blood level. Higher blood levels made a higher risk of those types of bleeds.

Q. Okay. But then they use the phrase might have contributed, so they are trying to figure out whether it did or not, right?

A. That's correct.

MR. MOSKOW: All right. Then the sentence goes on to say: But this cannot explain the apparent selectivity of the increase in major gastrointestinal bleeding with dabigatran for the lower gastrointestinal tract.

So I need to stop for a minute.

Q. What did the RE-LY trial show about the risk of major gastrointestinal bleeding between Pradaxa and warfarin?

A. So that there was a difference first off just generally overall in GI bleeding. Pradaxa had more than warfarin. But when you looked at where the bleeds occurred in the gastrointestinal system, high up in the system versus lower in the system, that there was a difference with the way the patients on Pradaxa versus the patients on warfarin were. There were many more lower GI bleeds in people on Pradaxa as

compared to people on warfarin.

So there seemed to be something different about the pattern of GI bleeds. Where they occurred appeared to be different, and the risk was higher for lower GI bleeds with Pradaxa as compared to warfarin.

Q. And we're going to come back to that in one moment.

Overall was there a percentage increase in major gastrointestinal bleeds on warfarin versus Pradaxa?

A. Yeah, overall a 50-percent increase.

Q. Okay. And so this is saying to the jury, we can't explain the fact that it's just -- that there's an increase in the GI tract, just age?

A. That's correct.

Q. And then they look for reasons why?

A. That's right.

MR. MOSKOW: Okay. So dabigatran has a low bioavailability after oral ingestion, and it is possible that metabolism of dabigatran etexilate by asteraceaes leads to progressively higher concentrations of the active drug during transit of the gastrointestinal tract.

Q. First of all, did I read that correctly?

A. You did.

Q. Could you describe it to me like I'm a high school student?

A. Okay. So going back to that picture we drew. I talked

about the fact that when Pradaxa goes into your mouth, the pill, and it gets into your stomach and your gut, your gastrointestinal system, very little gets absorbed. Most of it stays in your gut. Most of it stays in your GI tract.

And I mentioned to you that when it's in the GI tract, it can go from the pro-drug to active drug. So it can go from dabigatran etexilate to dabigatran. So that is what that is pointing out. That is talking about because it has a low bioavailability, only 3 to 6 gets in, 93 to 97 goes out directly into the gut. That, and the fact it can be metabolized in the gut, means you're having a higher concentration of active drug.

Whereas for warfarin, which is almost all absorbed and is metabolized in the body to make drug that is not active as an anticoagulant, if that ends up in the gut, that stuff gets excreted in the gut. It's not active locally like Pradaxa. That's what they are talking about. There's a difference between the concentration of the active drug in the gut with Pradaxa versus with warfarin, and that could explain the difference.

MR. MOSKOW: Your Honor, I have about 10 minutes left with this document, and then we can break.

Is that all right?

THE COURT: Yes.

MR. MOSKOW: Thank you.

Q. So the fact that we have this unabsorbed Pradaxa in the gastrointestinal tract, in the gut, what is going on with that? What is happening?

A. Okay. So that's the concept of understanding that in order for a drug to have an effect in your body, it needs to get somewhere. So it's called a local effect versus just an effect due to the fact that it circulates throughout your entire body.

Q. And do these authors identify that?

A. Yes.

MR. MOSKOW: Could you go to the next paragraph on the right? Actually just the very top paragraph on the right.

And so what these authors said is: Thus, local effects of dabigatran on diseased mucosa could account for the relative increase in lower gastrointestinal bleeding seen with dabigatran compared with warfarin in elderly patients in the RE-LY trial.

Q. Again, what is that telling us?

A. So it's telling us -- because remember I told you the drug can be activated in the gut. If it is activated in the gut, and it is sitting in the gut, it's passing through the gut, it has the ability to lead to an anticoagulant effect or a bleeding event if there is some -- something that has been damaged in the gut.

So the other part we didn't read into the record was there is different kinds of problems people have in their GI tract as they age, and they can lead to the tissue being damaged. So now you have damaged tissue or diseased tissue, and you have a high concentration of this dabigatran that is an anticoagulant, it can act right there. It doesn't have to get into the bloodstream and be carried there.

Because, again, bleeding events with this are going to tend to be occurring either at a site of injury or a site of a problem with the blood vessel. That is what leads to the bleeding events.

MR. MOSKOW: If we could go back to page 4 in this paper. That whole right-hand column from Site of Major Gastrointestinal Bleeding down.

Q. So do you see at the very top it says Site of Major Gastrointestinal Bleeding?

A. Yes.

Q. And then it does some numbers as to where they are in the Pradaxa folks and where they are in the warfarin folks?

A. Yes.

Q. Have you worked through that to try to figure out how that plays out in actual differences in bleeding rates?

A. Yes. I -- you can take this data from this paper, and you can actually just show with numbers how much the risk was increasing.

Remember we talked about doubling the risk for bleeding events overall as blood level goes up? We can find a number that shows how much the bleeding risk in the lower GI tract goes up based on the data that was collected.

Q. Can you walk me through that with the jury? In the interest of time, I'll do it right here.

A. Sure.

Q. Okay. So we have --

A. Two columns maybe, one for Pradaxa and one for warfarin?

Q. Oh, sorry.

A. I can't see --

Q. All right. So Pradaxa and warfarin.

Let's say for the sake of argument for doing this, we have 100 bleeds on warfarin.

A. Right.

Q. Based on the data, GI bleeds, right? These are GI bleeds?

A. Yes. Let's focus on that.

Q. All right. That's a G, not a 6.

All right. So based on the data in RE-LY, how many Pradaxa bleeds, GI bleeds would you expect?

A. Since it increased it by 50 percent, if you had 100 bleeds on warfarin, you would have 150 bleeds on Pradaxa.

So 50 -- so half -- 50 percent of 100 is 50. So 100 plus 50 means you would predict 150 bleeds with Pradaxa

patients.
Q. All right. So based on the data in that paper, what percentage of the bleeds, the GI bleeds on warfarin were in the upper GI tract?
A. So to make it easier, it was 53 versus 47. Let's just pretend it's 50/50.
Q. I asked about warfarin.
A. Oh, I'm sorry. Yeah. Yeah.
So it's 50/50 -- for warfarin it's 25 percent in the low -- upper GI tract, and 75 percent in the -- yeah, that's right -- in the lower. So if you take 25 percent of 100, that's 25. And if you take 75 percent -- no, that's the opposite actually.
Q. Oh.
A. No, no, no.
Q. I did it backwards. I'm sorry.
A. Yeah.
Q. It's hard to follow direction, isn't it? Sorry.
A. Right.
Q. All right. So this is upper GI and then lower GI.
A. Right.
Q. So upper GI --
A. 75 percent for --
Q. -- 75 percent --
A. -- warfarin.

Q. -- equals 75?
A. Right.
Q. And lower is 25 percent?
A. Right, which will be 25 bleeds.
Q. All right. Now how about on Pradaxa?
A. Pradaxa was about 50/50. If you want to do the math, we can. But it was 53 percent versus 47, so let's just say about 50 in the upper and about 50 in the lower.
Q. I'll write 53, but for purposes of this we're going to say 50 percent?
A. Yeah. I think it's the opposite, there were more in the lower than there were in the upper, but maybe it was that way. Look at the data.
Q. You have the paper in front of you, Doctor.
A. Hold on.
Q. It's on page 4, site of major bleeding.
A. Yes, you're correct.
Q. Okay. And so 50 percent of 150 is how much?
A. 75. So half of 150 is 75.
Q. Okay. And what about the lower GI, how many -- what percentage of those bleeds?
A. It was 47, but we'll pretend it's 50 for the math, the ease of math. And, again, it would be 75. So half of the bleeds in the upper and half of the bleeds in the lower.
Q. So what is this calculation telling you about the

similarity or difference in bleed rates between Pradaxa and warfarin in the GI tract?

A. So if you look just in the -- you see in the upper GI tract 75/75, there is about the same level of risk seen. But instead what is happening in the lower GI tract, that is driving the difference in the two drugs, and there is three times increased risk -- 25 times 3 is 75. So three times an increased risk of a lower GI bleed when you take Pradaxa. So this data in RE-LY was able to be looked at that way.

Q. And why is that important to the opinions that you're talking to the jury about today?

A. Because it's entirely consistent with what you might expect to happen based on what we know about this drug. This is a drug that has that low bioavailability. A lot of the drug can accumulate in the gut. This idea of a greater risk to the lower GI system is consistent with that biology or the way the drug acts.

So as a pharmacologist, I'm always interested in being able to understand whether or not what we know about the drug as far as the high concentration locally fits with what they saw in patients, and it does appear to fit.

Q. Now we didn't do the exact math, so it's not actually three times, right?

A. No, it's a little -- it's going to be a little bit different than three times.

Q. Okay. But what does it mean to you as a scientist that there is a multiple, it's more than two times increased risk of lower GI with Pradaxa versus warfarin?

A. To me that means this difference I'm seeing is, again, not likely due to chance, but indeed is likely due to something about the drug. And based on what we know about the drug, in my opinion, that something is this issue of high local concentration.

And that's consistent with what Dr. Eikelboom and colleagues are discussing in this paper. This is the thing that they described. I think we read that.

Q. Okay. And when we looked at the first page of this exhibit, you had indicated that it was published back in 2011?

A. Yes.

Q. Can you just very briefly, before we go to the lunch, identify for the jury every study that BI has done looking at this issue of why there are almost three times as many lower GI bleeds on Pradaxa than warfarin?

A. I have seen no such study. I'm not aware of any having been done, so it's an easy question for me to answer.

Q. Have you looked?

A. I did look. I looked in the literature, and I also looked within the company files. I find discussions of the need to do a study within the company files, but I don't

find any studies that were actually done.

MR. MOSKOW: And we'll look at that when we come back from lunch.

THE COURT: All right. We're going to take our lunch recess. Dr. Plunkett, you may step down. Don't discuss your testimony with anyone.

We'll recess -- is about an hour enough time for you? Is that all right? We'll see how it goes. I'd like you back here at 1:15.

Again, if you will remain in the jury room while you're in this building. You can leave things back here, come and go as you like from this room. Don't discuss the case with anyone. Don't start deliberating.

We'll start back at 1:15 with Dr. Plunkett.

THE COURT SECURITY OFFICER: All rise. This court stands in recess.

(Lunch recess taken at 12:11 p.m.)

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HUNTINGTON, WEST VIRGINIA

THURSDAY, OCTOBER 4, 2018, 1:18 P.M.

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(Jury not present.)

THE COURT: All right. Are we ready for the jury?

MR. MOSKOW: Yes, Your Honor.

THE COURT: Bring them out, please.

(Jury present.)

THE COURT: All right. Be seated.

All right. We're ready to resume your examination of Dr. Plunkett.

MR. MOSKOW: Thank you, Your Honor.

Good afternoon, everyone.

DIRECT EXAMINATION (Continued)

BY MR. MOSKOW:

Q. Good afternoon, Dr. Plunkett.

A. Good afternoon.

Q. When we broke for lunch, I had just asked you about studies that have been done looking at the way Pradaxa works in the gut.

Do you recall that?

A. Yes.

Q. And you, in your answer, mentioned that you were aware of some internal discussions about that issue; is that right?

A. Yes.
Q. Could you turn you to Exhibit 21 in your book? It's probably way at the front.
A. Oh, I'm sorry. I have 21 on one side, and 600 on the other. I'm sorry.
Q. I recycle tabs, so that's my fault.
A. No, no. That's okay. I'm there.
Q. Great.
Is this a power point about one of those discussions?
A. Yes.
MR. MOSKOW: Your Honor, I'd move 21 as a full exhibit.
MS. JONES: No objection, Your Honor.
THE COURT: You may proceed. It's admitted.
(PLAINTIFFS' EXHIBIT 21 ADMITTED INTO EVIDENCE.)
MR. MOSKOW: May I publish?
THE COURT: Yes.
MR. MOSKOW: Thank you, Your Honor.
Q. What is it about this particular power point that you thought was interesting?
A. So it's a discussion of a meeting with the company with some -- an advisory board, and they're talking about these issues of GI adverse events. So they are specifically talking -- one of the objectives was to manage those events, and then they are talking about -- on the second page, they

are actually talking about some studies they could initiate.
Q. Okay. Why don't we go to the second page of this document, which is the slide about a GI advisory board meeting, 16 December 2011, in Toronto, Canada. Right?
A. Yes.
Q. All right. So, first of all, can you explain to the jury, who is not in the pharmaceutical space like you are, what these advisory boards do?
A. So most companies that are large have these kinds of things. A company will often seek outside advice from doctors that are specialists in particular areas. So in this case, they're looking for people who have an interest or experience with gastrointestinal disorders. So they'll go to those individuals, and they'll talk about maybe drug issues that have been raised. And I've seen this done with other advisory boards for other issues for other drugs.

And they'll talk about the drug, and they'll get recommendations from the board based upon the presentations that they make about what they could or couldn't do, what makes sense to look at, hypotheses that they could or couldn't test, whether or not there's something missing. Sometimes that's the issue, is there something more missing that we need to pay attention to?

MR. MOSKOW: I don't know if you can read it, but could you pull out the very, very bottom where it says

confidential, and there's the line? Great.

Q. When you were reviewing this document, what if anything did you take from the fact that this was being presented at a Pradaxa senior executive committee meeting?

A. It tells me that this is an issue that is of importance to the company about their drug. And Pradaxa was a very important drug to the company, so it makes sense that any advisory board issue dealing with an issue for that drug would be one that would be raised.

And I think there's even deposition testimony that talks about the role of these -- this board, who was generally on it, things like that.

Q. And if I'm going too far into your memory, just tell us, but do you have an understanding as to the types of folks who were on this senior executive committee?

A. I can't give you all of the names, but certainly it was senior people within the medical group. Dr. Friedman, somebody like that. But I imagine Dr. *Varner was on there as well, but I don't recall whether he was.

But it was essentially the people that make decisions about the drug, that's who this was.

Q. Okay. And I want to focus on the objectives, those little hash marks.

The first objective, the optimal management of GI related adverse events and GI related bleeds, do you see

that?
A. Yes.
Q. From your review of the internal company documents from literature, from labels, what did you understand or do you understand was going on with regard to management of GI bleeds in the first year after the drug was approved, so between, you know, October 2010 and December 2011?
A. So the information I have seen shows the company was trying -- was looking at this issue, because this was an issue where it was -- it was not as good as warfarin in this one area.
Q. Why wasn't it as good as warfarin in this one area?
A. Based on the results of the RE-LY trial. So the RE-LY trial had shown that there was -- we did that calculation, a 50-percent increase overall --
Q. Okay.
A. -- in those types of bleeds.
Q. At -- in December of 2011, was it possible to treat bleeds related to warfarin differently than bleeds related to Pradaxa?
A. Yes, it was.
Q. Can you explain to the jury why?
A. So the drug Pradaxa in this time period had no I will use the term antidote. There was no agent to reverse bleeding. Whereas for warfarin, there was a way that you

could take the patients that were bleeding and give them vitamin K, which was a way to hopefully stop the bleeding and reverse the effects of Pradaxa. I'm sorry, of warfarin.

We had no similar agent for Pradaxa, so you had to just wait until the Pradaxa cleared from the system. There was no drug you could give that would reverse the specific effects of Pradaxa as there was for warfarin.

Q. So what significance was there, if any, for the company to look at ways of preventing those bleeds in the first place?

A. Well, since you can't reverse them, the issue would be what can we prevent so that we don't have that risk. Knowing that our patients are in a greater risk of these type as compared to warfarin, what can we do to prevent? And so the issue was understanding what they can do.

Q. And that next bullet point says essentially that, right, assessment of risk minimization strategies regarding their occurrence?

A. That's correct.

Q. And a simple way of saying that, let's look at ways to stop bleeds?

A. Yeah, look at ways that we can prevent them from occurring.

MR. MOSKOW: Okay. Let's go down and look at some of the key messages here. The second bullet point, more

data on the GI effects of Pradaxa are required to enable recommendations of clinical practice as the current evidence base is limited to draw fair conclusions.

Q. Based on your review of the literature and the documents as of December 2011, was that a true statement?

A. Well, not really. I think the RE-LY data had data that gave them an answer about what was going on generally from the clinical picture, but they certainly didn't -- hadn't delved into a lot of the details on why. Although, the Eikelboom paper gave a discussion of what could be going on.

Q. And the Eikelboom paper was published in or about this time, right?

A. That's correct.

Q. Is the interaction -- well, let me say it differently.

Does the Pradaxa in the gut that you talked about, that local effect, is that something that is spoken about in the Medication Guide?

A. No.

Q. I want to go to this next point, specifically information on how to dabigatran interacts with the GI tract is lacking.

Was it lacking in 2011?

A. So they had some information, I would argue, that they knew that -- they knew that it was metabolized by esterases, and they knew that you would have active

dabigatran. And they knew at this time that 80 percent of the dabigatran in the GI tract was activated. They had done a pharmacokinetic study that had looked at that issue. So they knew that they had lots of active drug in the GI tract, so that they knew. And they know what the drug does generally.

So I don't think it's an issue of not understanding basically what's going on, but certainly they hadn't figured out how to prevent it. That is true.

Q. Do you take issue with this statement that says specifically information on how dabigatran interacts with the GI tract is lacking?

A. I do. Based on the data I have, yes.

Certainly can we know more? We can always know more, it is always better. But they did have some basic information that explained, in my view as a pharmacologist, what was generally going on.

Q. That's a next transition, you can always know more, so let's go to the next slide, please.

And the next slide reflects the activities that are proposed or recommended, right?

A. Yes.

Q. Have you participated in advisory boards like this?

A. Not for a large drug company, no. But I've done similar things for some of my smaller companies, yes.

Q. Okay. And these activities, proposed, recommended, do some people call them take-aways?

A. You could, yeah, a message to take away.

Q. Okay. Let's look at the very last bullet point, and we'll move on, initiate research activities to investigate dabigatran effects in the GI tract.

A. Yes.

Q. Okay. So what is -- what could be initiated to investigate dabigatran effects in the GI tract?

A. There's all kinds of studies they could do. They could do an animal study. They could also do some more clinical work to look at more detailed issues on where the drug -- how much the drug is ending up in the GI tract repeatedly.

There's things they could do. They could do things at a molecular level to look at taking cells -- they could put cells in a test tube and in a Petri dish, and they could look at the way that dabigatran interacts with cells at that molecular level as well. Yeah, there is things they could do.

And so certainly, again, I would not -- I would not suggest that not doing more research is not good. Absolutely more research would be good, especially on the issue of is there a way that they could prevent this from happening.

Q. Where, if ever, has BI compared the Pradaxa

gastrointestinal issue, and particularly lower GI, and warfarin, looking at how the drug specifically interacts with the GI tract?

A. I haven't seen a study. I am not aware of one that they have.

Q. All right. Let's move on. I want to focus now -- I'd like to switch gears, and I want to talk about what Boehringer knew about its drug and about the patients who were taking it. Okay?

A. Okay.

Q. And in particular I want to start with something called the company core data sheet.

Do you know what that is?

A. Yes.

Q. Could you tell the jury what a company core data sheet is?

A. So it's a document that lays out everything that the company knows about their drug, specifically how it works, safety issues, risks, benefits. And it also includes statements of what they believe to be things that should be done. So they actually have information in there about warnings that should be given to patients, specific information. It lays it out in sections sort of like you would build a label.

Q. Okay. Is that an important document for someone like

you in this type of project?
A. Yes.
Q. Why?
A. Because it tells me -- even though I can look at the label and know what they have stated to the FDA and to the physician or in the Medication Guide to the patient, I can compare that with what is in the core company data sheet from the same time. And that's the issue of what did they know that they weren't conveying to physicians and to patients. So it allows that comparison.
Q. How does a company construct a company core data sheet? In other words, where does the information come from?
A. It's all their testing, the studies that they've done, and that's why changed over time.

So, in this case, you'll see Pradaxa's core company data sheet change from year to year as new studies were performed, new clinical data, new indications for the drug were gained, new adverse -- new experiences from once the drug is on the market, the risks or the toxicities that patients were experiencing. All of that can come into the data -- that particular document as it builds over time.

And, again, it's a -- this drug is sold worldwide, so it is a document that is not just experienced in the U.S. but experienced around the world.

Q. To the extent that the company core data sheet or -- can

we call it the CCDS just to make it easier?
A. Sure.
Q. Okay. To the extent that the CCDS includes information from people outside of the United States, data from people outside of the United States, is it still relevant to people here in West Virginia?
A. Absolutely. I would consider a lot of it to be very, very relevant.
Q. Okay. But what is it about human anatomy generally, if you know, that is different from Europe to the United States?
A. There's nothing that should be different on this issue of why people bleed and why -- how you prevent strokes.
What -- the thing that can be different -- do you want me to explain?
Q. Sure.
A. The thing that could be different, if you had done a study in a population -- and this happens a lot in Asian populations -- only in people from Japan, and you wanted to say whether or not that information would relate to what you expect to happen in the U.S., which is a much more mixed genetic background, people from all different places, it may be that that study collected just in the Japanese population wouldn't tell you exactly what the risks would be in the U.S. people. And that's because there are known genetic

differences in Asians versus Caucasians or U.S. background people that can affect the risk of some drugs.

I don't believe that is true, however, for this drug based on the fact that it's not highly metabolized in the liver. And that's the main issue for the Asian population, whether or not it's metabolized the same way.

Q. So if I could turn you to Exhibit 351. It's probably now towards the back of your binder.

A. Yes.

Q. Okay. Are you able to identify that document?

A. Yes.

Q. And what is it?

A. It's this company core data sheet, CCDS, dated December 10th, 2009.

MR. MOSKOW: Your Honor, I move Exhibit 351 as a full exhibit.

MS. JONES: No objection.

THE COURT: It's admitted. It may be published to the jury.

MR. MOSKOW: Thank you, Your Honor.

(PLAINTIFFS' EXHIBIT 351 ADMITTED INTO EVIDENCE.)

MR. MOSKOW: All right. So do a little bit of teaching here for a moment.

Q. Earlier you wrote dabigatran etexilate on the screen, and you indicated what about that? Why does it have the

etexilate?
A. So that is so it will get absorbed. So that's what I call the pro-drug. So this is the form that on its own is not active. It has to get into the body, and once it's in, the etexilate comes off, and you have dabigatran which is active.
Q. Now, you chose the document dated 10 December 2009. Why is that time frame important to you?
A. So this is a document after the RE-LY study data has been collected, but it is before the drug was approved. So this would be what the company knew at the time that they were submitting the NDA to the FDA, because a lot of this data in here is what made up the NDA.
Q. Okay. So can I summarize that? This is what the company knew at the time they were applying to sell the drug?
A. Yes.
MR. MOSKOW: Okay. And we're going to bounce around in this a little bit if that's all right. Well, more if it's all right for Ms. Veldman.
But if we could drop down to the bottom of the page, there is several paragraphs under the word general, and I want to focus on the one in the middle. Do you see that?
There is a close correlation between plasma dabigatran concentrations and degree of anticoagulant

effect.
Q. Do you see that?
A. Yes.
Q. Can you tell the jury what that means?
A. That is those curves we were talking about. The more Pradaxa, the more in your blood, the greater the increased risk of bleeding. But also enough Pradaxa in your blood is needed in order to prevent strokes. It's that therapeutic range, issue that blood levels matter. That you can get information from the blood levels that tell you whether or not the drug is working and whether or not there is an increased risk.
Q. Where is that information that blood levels matter in the Medication Guide that is given to West Virginia patients?
A. It's not there.
Q. Further down in that same area, there is a paragraph that starts with however?
A. Yes.
Q. I really want to focus about halfway down at recommended. Do you see that?
A. Yes.
MR. MOSKOW: So it says: At recommended prophylactic doses of dabigatran etexilate, dabigatran may prolong the activated partial thromboplastin time, aPTT, and

the INR, but these tests are relatively insensitive to the activity of dabigatran and are unsuitable alone as measures of anticoagulant activity.

Stop there.

Q. Can you make that so I can understand it?

A. So this sentence is saying -- prophylactic means the dose to prevent. So at the dose people take to prevent strokes, that's what they're talking about. That there are some tests that could be used to try to understand whether or not the drug is producing the blood thinning effect. And those tests are the aPTT, and there is another one mentioned there, the INR. And the INR test is one, by the way, that is used for warfarin patients. It's the one people use.

But what they're saying is those two tests don't appear to be suitable in order to tell you whether or not there is adequate anticoagulant activity. Which means that it's not like the blood levels. The blood levels correlate, but these tests do not appear to provide that kind of information that allows you to know if you're at the right level of efficacy for the drug.

MR. MOSKOW: Okay. Moving on, it says: However, in patients who are bleeding, aPTT test may tell determine an excess of anticoagulant activity.

Q. Do you have see that?

A. Yes.

Q. All right. So it may not be sensitive, but if somebody has too much, this will tell us?
A. Yes.
Q. Okay. How do we know how much is too much?
A. How much is too much?
Q. Well, it says an excess of anticoagulant activity. Is an excess too much?
A. An excess is too much, and we know that from the RE-LY data. The RE-LY data had data that correlated this blood level data with too much Pradaxa, which would be the increased risk of bleeding. So too much anticoagulation, too thin of a blood, you increase your risk of bleeding.
Q. This idea of excess, is this the only place that the company talks about excess amounts of the drug?
A. No. There is a number of -- there are other places within this document, other versions of the document, and also some other documents that are available in other questions that use the words excessive dabigatran exposure, which is another way of saying too much Pradaxa.
Q. Where does that language, any of the ways you've just described it -- either excess dabigatran exposure or too much Pradaxa or excess anticoagulant activity -- where does that kind of language appear in the patient Medication Guide in the Pradaxa information given to West Virginia residents?
A. Unfortunately it is not there.

Q. If we could move to page 10, please, and I want to focus at the bottom of the page, co-medication.

A. Yes.

Q. So there is something here that says co-medication with P-gp inhibitors. Do you see that?

A. Yes.

Q. And what is a P-gp inhibitor?

A. So I didn't draw that on my graph, my Mr. Bill man or the gingerbread man. I didn't draw that but essentially a P-gp -- P-gp is a protein that is present in your gut, in the lining of your gut, and it is there to transport drugs in and out of the blood. So when the drug is absorbed into the blood, this transporter can move it back out to the gut. So it is actually -- if something comes in, it's taking it back out.

So if you inhibit the activity of that transporter, which we know Pradaxa by the way interacts with -- we know Pradaxa moves with this transporter back out of the blood back into the gut, if you inhibit it, that's going to prevent the Pradaxa from leaving, and you're going to -- you could increase your blood levels. And this is true for any drug that interacts with this transporter.

Lots of drugs interact with P-gp as a transport mechanism. But the reason it's really important for Pradaxa is that issue we went into, a very small change in the

absorption. So if you can't get it back out, that 3 percent could be 4, 5, 6 percent now because you inhibited that activity. So that could lead to, ah, unsafe levels or high levels, too much Pradaxa in the blood.

Q. So does everybody in this room have P-gp things working?

A. We should. If you're a normal person, you have that in your gut, and it's there, again, to protect your -- protect your system to some extent.

Not all drugs interact, so P-gp transport isn't an issue for all drugs. But it is for Pradaxa as well as a number of other important drugs used to treat cardiovascular diseases.

Q. You beat me to the punch.

So are there P-gp inhibitors that people with cardiac issues typically are on?

A. Yes.

Q. Why is that?

A. That is because most people that have atrial fibrillation will have some other condition, too. So it's -- because, first off, you tend to be elderly. So you might be a taking blood pressure drug, or you might be taking a drug actually to treat that atrial fibrillation. It's called an antiarrhythmic. So now we are not trying to prevent clotting, but you are taking the drug to actually make it so your heart doesn't beat so fast, the atrium.

So those kinds of drugs are used at the same time as an

anticoagulant, so if you have medicines together. And it's very common for people with atrial fibrillation to have more than one drug on board.

Q. There is a statement here about a drug called verapamil. Do you see that?

A. Yes.

Q. And what is verapamil?

A. Verapamil is -- well, first off, it has the ability to inhibit the P-gp, but it's an antiarrhythmic drug. So it's one used to treat these irregular heartbeats. It is used for that purpose.

Q. Are there other drugs that are commonly used in AFib patients that are similar to verapamil?

A. There is others commonly used that might have a little bit different mechanism of how they change the heartbeat, but they're used for the same reason. So amiodarone is the name of a drug that is also an antiarrhythmic, so changes that -- it is used to treat atrial fibrillation.

There is also a drug called carvedilol or Coreg. It's a drug that is used for blood pressure, but it also slows the heart, so it is also used in patients with atrial fibrillation as well as patients that may be taking it for hypertension.

Q. And one of the things, talking specifically about verapamil, is that it has this line, increase of Cmax by 180

percent and AUC by 150 percent. Those are technical terms.

What is Cmax?

A. So Cmax, peak, we had the peaks over there on the curve, that's the maximum concentration in blood. That's a peak level. So Cmax and peak, we can use those interchangeably.

Q. So when you wrote peak here, that would be Cmax?

A. Yes.

Q. And then what is this AUC?

A. AUC stands for area under the curve. So up there if you were to take a pen and shade -- just do the single dose, it will be easier. If you were to shade all of that information right under that, that would be the AUC. You can use a mathematical formula to calculate how much area is taken up.

Just like in geometry class we can figure out what area of a circle is, here we can use a formula to figure out what the area is covered by that. And that area under the curve is a measure of all of the -- the amount of drug that your body has been exposed to.

So -- because, again, it's all -- the entire time it is in your body, from the time you take it to the time you get it out. So when you measure the area under the curve, that's a measure of your total exposure to the drug. Versus the Cmax just tells you what the highest level was. So you get additional information when you look at how much the

total exposure was.

Q. So what is this information telling us about how verapamil affects the amount of Pradaxa in the blood?

A. It's going to increase it. So, in other words, again, when those two drugs are on board at the same time, if somebody takes Pradaxa and is on verapamil, then they're going to have a higher level of Pradaxa in their blood. So they could have excess of exposure to Pradaxa.

Q. Now is this something that is already included when somebody has bad kidneys, or is it in addition to that?

A. Oh, this is in addition. Those are different things.

So a P-gp inhibitor, this drug verapamil or, like I said, other drugs, they're increasing the level of Pradaxa in the blood by one mechanism that is not letting it go back out. So the kidneys is how the blood -- the drug leaves the blood through that organ.

Different things, so these are two different -- it would be -- it is essentially saying there's two different ways that we can increase the blood level of Pradaxa. One is by making it stay in at the start, and the other is by not letting it go out at the end. So it is like having a plug in the dike at two places.

Q. Is that important information for pharmacologists and toxicologists like you?

A. Absolutely.

Q. Why?
A. Because now we have multiple ways to increase the blood level. So if you have a patient who has severe renal impairment and is taking a P-gp inhibitor, then their blood levels are going to be even higher than if they were just just severely renally impaired or just on the P-gp inhibitor.

In other words, the two things, it's not one plus one equals two on risk, it's one plus one equals five because the two things act together to increase the exposure. So that person's risk level for bleeding is even higher than the person on just the P-gp alone or the person who just had the renal impairment but wasn't exposed to the drug.

Q. Where is -- that information that you just described, that one plus one equals more than two, where is that information included in the patient Medication Guide for Pradaxa?

A. It's not. It's also not included that way in the labeling for the physician either.

MR. MOSKOW: Could we go to page 13, please. I want to focus your attention on the bottom half of the page where it says renal impairment. Let's just take out that -- okay.

Can you all read that from where you are? Should I make it bigger?

So at the top there is a statement: There are no

data to support use in patients with severe renal impairment less than 30 milliliters a minute creatinine clearance. Treatment in this population with Pradaxa is not recommended.

Q. Correct?

A. Yes.

Q. What does it mean to say there's no data to support these?

A. Well, it means what I told you earlier. In other words, it hasn't been tested. It hasn't been shown that it could be used safely and effectively in patients with severe renal impairment.

And the RE-LY study did not -- it had a few patients that might have had severe impairment, but it did not have enough to draw any conclusions and to make any recommendations to doctors about -- about the issue and how that affected the risk in patients.

MR. MOSKOW: At the bottom of the second bullet point, you'll see there's a paragraph: Regular assessment of renal status is required in these patients.

And then: A coagulation test, such as aPTT, see warnings and precautions, monitoring and laboratory tests, may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure.

Q. Do you see that?

A. Yes.
Q. I want break that down.
First of all, based on your review of the medical literature, internal company documents, does it make sense to regularly assess kidney function?
A. Yes. With this drug, absolutely because of the -- how it relies so much on being excreted or being eliminated, getting out of your blood that way.
Q. Okay. And then it says a coagulation test. So what's a coagulation test?
A. So that is a test that's going to tell you whether or not your blood is too thick or too thin. So for warfarin, it's an INR. Here they're talking about using this aPTT. That's just another test that can be done, a different type, same end points. Is the blood too thick, too thin.
Q. Is that the same test being done to look at the kidneys?
A. No. Well, it's a different test, but it can be done with the same blood sample. So you take a sample of blood, and you could do two things with that blood. But it's a different test, yes.
Q. Okay. So if I'm monitoring kidney function, explain to the jury how I can figure out just by monitoring kidney function whether somebody has this excessive dabigatran exposure, too many Pradaxa.
A. So you'd have to take a blood sample from a patient in

order to look at their creatinine clearance, which is the way they monitor it. So if you take that blood sample, you can take part of that blood sample and use it to run one of these tests, like the aPTT. That's what they're saying. That's the test they're mentioning here.

So, yeah, it wouldn't be another stick. It would be at that time that you're monitoring their kidney function, you could also be looking at whether or not their blood levels of Pradaxa are too high. Because that test gives you an idea that it's -- that you have too much Pradaxa in your blood even though it doesn't tell you the exact number.

Q. As of 2013, did the patient Medication Guide talk about getting regular assessment of renal function of kidneys?

A. In 2013?

Q. Yeah.

A. It has a statement about kidney function, yes. It wasn't exactly like this, though. It didn't put things together. But certainly it did mention that, yes.

MR. MOSKOW: If we could drop down to the top of page 14, please. I just want to focus on this formula here.

Actually I probably should have started on the other page, but that's okay. Are you able to pull the bottom of 13? Thank you.

Q. So as part of determining whether somebody has bad kidneys, are there formulas that doctors and scientists use

to figure that out?
A. Yes. That's -- they would take the number from the blood test on the amount of creatinine, and they would use that in a formula, which is in this document. They give it for men and women separately.
Q. Are there more than one way to calculate somebody's kidney function, the way their kidneys are working?
A. Yes.
Q. Are there differences between them?
A. Well, there's different methods and different formulas. There are, but this one here is one that you see described in the literature a good bit.
Q. If you know, was this particular formula used for the patients in the RE-LY trial?
A. That I don't know. I haven't done that comparison.
Q. Okay. But it indicates right here: Creatinine clearance can be estimated using the Cockroft-Gault formula as follows. Right?
A. Yes.
Q. And then there's a different calculation for men and for women. Do you see that?
A. Yes.
Q. Why is that?
A. Because of this issue we already talked about, the issue of men and women having different physiologies to some

extent. They have a different blood volume. They have a different -- because of their body size and just their basic who they are, there is differences that affect the way your kidneys work and also the way -- how much volume there is in your body for things to circulate within. So that is why you have to do this correction for -- this formula for females versus males.

Q. Okay. You indicated to the jury, when you were telling them what a CCDS is, that it changes over time.

A. Yes.

Q. Why is that?

A. Because once -- when you have new information, you put it in. So, in other words, if you gather new data or have new observational data, you do. So this company indeed they have later CCDSs where there is additional information added that tell us something more that they've learned about the safety of the drug or the way the drug works or what kinds of risks they've seen in patients.

Q. Okay. Did that happen with Pradaxa?

A. Yes.

Q. Turn to Exhibit 1, please.

A. That one is the first in the binder.

Q. What is Exhibit 1?

A. It's a company core data sheet with the date of -- for Pradaxa from the date of December 18, 2013.

MR. MOSKOW: Your Honor, I would move Exhibit 1 as a full exhibit.

MS. JONES: No objection, Your Honor.

THE COURT: It's admitted. It may be published.

MR. MOSKOW: Thank you, Your Honor.

(PLAINTIFFS' EXHIBIT 1 ADMITTED INTO EVIDENCE.)

MR. MOSKOW: So you had indicated this is 18 December 2013.

Q. Does this document include data going back to all of the clinical trials or is it just what's going on right here in December of 2013?

A. No, it's a -- I would call it a living document. In other words, they take what they know, and they add to it.

Now if they found something was wrong, you know, I imagine they would take that out. But certainly it has all of the information, so it gets bigger. You will see more information. More data, more -- more instructions and things like that will appear as the document grows over time.

Q. Okay. And one of the things I want to point out to the jury is that there's a color code now. Do you see that?

A. Yes.

Q. And what's significant about that?

A. So by 2013, in addition to the use of the drug in patients with atrial fibrillation -- and that's that blue

bar, SPAF -- they had obtained three additional approvals for uses in other types of conditions. So they had submitted a separate application that was approved for VTE, which is venous thromboembolism. It's another disorder where you need to prevent clots. And the same thing for the pink and the purple, those were other indications where you need an anticoagulant. So different clinical data was collected, different studies, different populations of patients.

Q. Okay. At the bottom there is something in white. Do you see that?

A. Yeah.

Q. And it says all indications.

A. Yes.

Q. So what parts of this company core data sheet should the jury be looking at if they want to know about prevention of stroke in atrial fibrillation patients?

A. So you would go for the white boxes because that applies to every patient population. And then you would look at the blue boxes for the atrial fibrillation patients.

Q. And with that in mind, could we turn to page 4, please.

You see there's a -- sorry. There's a white box in the middle that says reasonable impairment?

A. Yes.

Q. All right. So I want to start there.

And actually, can you read that first paragraph slowly to the jury, please?

A. Sure.

Renal function should be assessed by calculating the creatinine clearance, CrCl, prior to initiation of treatment with Pradaxa to exclude patients for treatment with severe renal impairment. Then they say, for example, CrCl less than 30 mils per minute. There are no data to support use in patients with severe renal impairment, in parentheses less than 30 mils per minute CrCl. Treatment in this population with Pradaxa is not recommended. See contraindications.

Q. Okay. Is that information that you wanted to call to the jury's attention?

A. Yes.

Q. Why?

A. Because this is the exact issue in this case. It's the idea that they're talking about the -- there is -- there is no data to support use in this patient population with severe renal impairment, and that's the patients that are getting the 75-milligram dose in the U.S.

Q. So at this point in 2013, the Pradaxa 75-milligram dose had been sold in the United States for almost three years?

A. Yes.

Q. And what significance, if any, is there to your opinions

in this case that the company is still reporting in their core company data sheet that there is no data, no information to support that use?

A. Well, there is at least two things.

Number one, the fact that there is no data means they haven't done any additional studies to provide that data. And I would say that based on three-year period having elapsed, I think that that is a problem. The company wasn't doing the job they should do to provide data for patients.

However, what's interesting here is in this document they're actually contraindicating, ah, the use of the drug in those patients, and yet in the U.S., they're selling a dose without data in the same population.

Q. I wanted to ask you about that.

So what this said up here is that you want to exclude patients for treatment with severe renal impairment. But that's not true in the United States. There's actually a dose for those folks.

A. That's correct. And that was -- that was mentioned -- this document is a worldwide document, so there is different -- different ways that this drug is used in countries outside of the U.S.

Q. What, if any, concerns do you have about a product that is contraindicated for patients with severe renal impairment outside the United States, but for which a 75-milligram dose

is being sold without data to support in patients with severe renal impairment?

A. My issue would be if you're going to do -- if you're going to do that in the U.S., you need to let doctors know this exact issue, that there is no data to support -- that has been collected to show that that drug is safe and effective. And I think they should have been doing studies to prove that safety as well, if they're going to continue to sell it that way.

Q. Now you indicated that there was a contraindication. You specifically called that out in looking at this paragraph, correct?

A. Yes.

Q. All right. So this comment, see contraindications, your use of these documents, what does that mean?

A. So that is a section within the labeling, not in the Medication Guide. It won't be spelled out that way for the patient. But in the physician, the label to PCs, there is an actual section called contraindications. And that's the information within the label that tells the physician don't use -- the risks outweigh the benefits in these type of people. That's what contraindication means, don't use it, risks outweigh benefits. And that's the decision that's made in order to put a contraindication on a label.

Q. And within this company core data sheet, what the

company knows and believes its drug, what does it mean when they write see contraindications in this document?

A. In my opinion, it means that they understand that it should be contraindicated. And I would --

Q. I was being more basic.

What am I supposed to do now?

A. Oh, I'm sorry. You are supposed to go to that section of the label if you would like to see more details. I'm sorry.

Q. Very good. So let's go to page 9, contraindications.

And here it specifically notes at bullet point two, severe renal impairment, right?

A. Yes.

Q. Based on your work with labels and regulatory documents and company core data sheets like this, what does it mean when you contraindicate something?

A. That was the answer I was giving. When you contraindicate means you have decided that the risks outweigh the benefits. So there really is no reason to use the drug in this population because of the risk it poses. So it's an unacceptable or unnecessary risk that you're putting the patients at at this point in time.

Q. On that same page, there is a spot at the bottom that says special warnings and precautions and haemorrhagic risk.

Do you see that?

A. Yes.
Q. What is haemorrhagic risk?
A. Bleeding risk. Hemorrhage is the bleed.
Q. And does Pradaxa have a bleeding risk?
A. Yes, it does.
Q. Okay. Are you able to kind of summarize in your own head the way it's worded in the patient Medication Guide?
A. It tells -- tells patients that it's a serious risk and may be -- may cause death. So patients on Pradaxa are at a risk of bleeding, and that bleeding can be fatal and lead to death, I believe it says.
Q. And we're going to talk more about that, but that sounds like it includes everything. It includes I could bleed or I could die from a bleed.
A. Well, it's a serious warning. I mean, I'm not saying it's not a serious warning. But it's not giving everything, all of the information that a patient needs to understand about the drug.
Q. Is there information in this section in the CCDS that makes you think, you know, there could be more in the warning?
A. Yes.
Q. Okay. Let's keep going, then.
MR. MOSKOW: Turn the page to page 10. And I want to start in the second white box, the third paragraph where

it says factors.

Q. Do you see that?

A. Yes.

MR. MOSKOW: And I'll read this, and then I will have some questions for you.

It says: Factors such as decreased renal function, 30 to 50 milliliters creatinine clearance, age greater than or equal to 75 years, or strong P-gp inhibitor co-medications are associated with increased dabigatran plasma levels. The presence of one or more than one of these factors may increase the risk of bleeding.

Q. Do you see that?

A. Yes.

Q. Is that important information?

A. Yes.

Q. Why?

A. It's that issue I was talking about, one plus one equals two or one plus one can be five. It's the idea you put more than one factor, like the P-gp inhibitor and the severe renal impairment, and those things together could put people into the issue of having too much Pradaxa in their blood and an increased, unacceptable risk of bleeding.

Q. And how would you know that? How do you know if you have these things whether or not you have too much Pradaxa?

A. The only way to know is to actually measure your blood

levels, and that's the most information. We haven't talked about it much, but it's really important that patients understand there is a way to know if you're at risk, just the way it is important for doctors to know there's a way to make the drug safer for their patients.

MR. MOSKOW: Let's look at the top box on this page. And there is a paragraph that says tests of anti -- oh, sorry -- tests of anticoagulant activity.

Do you see where I am?

THE WITNESS: Yes.

MR. MOSKOW: And it says: Tests of anticoagulant activity such as thrombin time, TT, ecarin clotting time, ECT, and activated partial thromboplastin time, aPTT, are available to detect excessive dabigatran activity.

Q. Do you see where I'm reading?

A. Yes.

Q. Once again, that phrase excessive dabigatran activity.

Can you tell the jury where this document information is in the Medication Guide that is given to patients in West Virginia so they can know whether they're getting too much Pradaxa?

A. It is not there.

MR. MOSKOW: Let's go to page 12, please.

Q. We talked a little bit about P-gp inhibitors before. Do you recall that?

A. Yes.
Q. Halfway down the page here, there is a section that says interactions.
A. Yes.
Q. And we are actually going to go further down, but do you see where it says interactions, and then there is more information right below that?
A. Yes.
Q. And it says P glycoprotein interactions?
A. Yes.
MR. MOSKOW: Can you bring up that second box below that? Great. Thank you.
Q. And P glycoprotein inhibitors, are those that P-gp inhibitor that we talked about a little bit before?
A. Yes.
Q. Could you read again slowly the paragraph that's up on the screen regarding P-gp inhibitors?
A. Sure.
It says: Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors, such as amiodarone, verapamil, quinidine, systemic ketoconazole, dronedarone, ticagrelor and clarithromycin, is expected to result in increased dabigatran plasma concentrations.
Q. Okay. Going back to the discussion we had about what

P-gp inhibitors do, can you explain to all of us what information this is telling us?

A. It's telling you that because dabigatran, the drug Pradaxa, interacts with that transporter, if you give dabigatran with one of these drugs that it is listing, you could end up with too much Pradaxa in your blood. You are going to increase the levels, and that could lead to too much.

Q. And based on your experience working with labels and company core data sheets and all of these documents that we've been looking at today, when the phrase such as and a list of drugs is given, what does that mean?

A. So the such as is telling you that these behind here are specific examples of P-gp inhibitors. So each of those drugs in there are ones that have been identified as inhibitors of P-gp.

Q. Okay. Is this an exhaustive laws of all the P-gp inhibitors?

A. No. And, in fact, it doesn't list some of the ones that have been classified as strong inhibitors that are drugs used to treat cardiovascular disease. I mentioned one earlier, carvedilol is an example of one that is not on that list. But it is also, like verapamil, a strong P-gp inhibitor that could be used in patients that have atrial fibrillation.

Q. Thank you.

MR. MOSKOW: Let me move your attention to page 20.

And I just want to pull out one sentence near the bottom of this box that says: There is a close correlation between plasma dabigatran concentrations and the degree of anticoagulant effect.

Q. We've seen that language before?

A. Yes.

Q. Again, where is that information in the product labeling and Medication Guide in the United States?

A. It's not.

MR. MOSKOW: And if I could turn you to page 33 of this exhibit. And I really want to focus on the special populations box.

Q. Do you see that, and then underneath that it says renal impairment?

A. Yes.

Q. You told the jury earlier about some small studies that had been done looking at Pradaxa in people with bad kidneys. Do you recall that?

A. Yes.

MR. MOSKOW: I want to focus your attention, then, on the second paragraph here.

It says: In a small number of volunteers with severe renal insufficiency, between 10 and 30 milliliter a

minute creatinine clearance, the exposure area under the curve to dabigatran was approximately six times higher and a half-life approximately two times longer than that observed in a population without renal insufficiency.

Q. Is that important information?

A. Yes, it is.

Q. Why is that?

A. So this information is telling you that when you have severe renal insufficiency, your blood levels -- your exposure could be six times higher. So, in other words, too much Pradaxa would be likely to be found in your blood.

The other thing that is important about this data is the size of the data. And you have to understand that this is the data that was the only data that was available to justify the 75-milligram dose that FDA used in its assessment. So you have to understand that that's what that data was used for.

It was used -- it wasn't in AFib patients. It wasn't -- it was only -- like I said, I think there were 11 people with severe insufficiency as compared to thousands of people that were studied in the safety and efficacy trials. And this was a population that was modeled to then use to justify that 75 milligrams would be used in patients with severe renal insufficiency.

Q. So did these people get the 75-milligram dose or not?

A. They did not. They got the 150, and then they looked at their blood levels. And then they used that with a computer model to say we want to approve the 75.

Q. Let's move on. I want to turn you to document 3295 in your -- you're going to have to look at it in there first, way in the back.

A. Way in the back.

Q. Do you recognize this document?

A. Yes.

Q. What is it?

A. This is a publication by Wessler and colleagues published in 2013.

MR. MOSKOW: Permission to publish, Your Honor?

MS. JONES: No objection.

THE COURT: It's admitted. You may do so.

MR. MOSKOW: Thank you, Your Honor.

(PLAINTIFFS' EXHIBIT 3295 ADMITTED INTO EVIDENCE.)

BY MR. MOSKOW:

Q. And is this a study that you wanted to talk to the jury about?

A. Yes.

Q. Why is that?

A. So when I first started my work on this case, this was a paper I found that talked specifically about this interaction of the P-gp transporter with different

cardiovascular drugs. So it's the issue of what drugs out there would be expected to inhibit the transport of Pradaxa so that it stayed in the blood and built up levels, so these kind of drug interactions.

So I looked in here, and it gives you a list of some of the commonly used cardiovascular drugs, and whether they were like verapamil, which is in the label, a strong inhibitor or not. And so there were other drugs in this list that are strong inhibitors like verapamil that are not specifically listed in the labeling for Pradaxa.

Q. Okay. And I want to focus on that in just one moment.

I wanted to start at the top of the page, the very top of the first page. It references the Journal of the American College of Cardiology. Do you see that?

A. Yes.

Q. We talked about that once before, that journal, right?

A. Yes. That's the same journal of the paper by Dr. Reilly, et al., that talked about blood levels of Pradaxa and the therapeutic range.

Q. Okay. And if we could then move to page 4 of this document.

Do you see at the bottom of the first page, there is an area that says oral anticoagulant?

A. Yes.

Q. And then it talks about dabigatran?

A. Yes.
Q. And then going over to the right-hand column, and then going on to page 5, I want to read something to you and have you work -- help us understand it. Okay?
A. Yes.
MR. MOSKOW: It says: P-gp inhibition and impaired renal function are two major independent factors that can increase dabigatran concentrations, with greater effects if both are present.
Q. Does that just mean that if you have both bad kidneys and a P-gp inhibitor, it's worse than having either of one of them alone?
A. Yes. And that's this issue of independent. So they have a -- they both contribute separately. Unlike earlier in the Reilly paper, they talked about how age and kidney function go together, that's not here. This is kidney function separate from the presence of a drug, and that's that one plus one equals two versus one plus one equals five.
Q. Okay. And then it says: Exposure to dabigatran increased with coadministration of the strong P-gp inhibitors, and then it gives several, right?
A. Yes.
Q. And it talks about verapamil as being one of them.
A. Yes, that's correct.

Q. If I could move you actually to the very bottom of page 5, the bottom right-hand corner.
A. Okay.
Q. Do you see that there is a -- there's another one that says: Carvedilol inhibits P-gp activity to a similar degree as verapamil?
A. Yes.
Q. Is that important information for you?
A. Yes.
Q. Why is that?
A. Because it has essentially the same effect biologically as far as its ability to inhibit that transporter. Yet the verapamil was one that was studied and put into the label, and carvedilol is not in the label. So physicians and patients wouldn't know, based upon what's in the label, that carvedilol was a drug to be avoided even though verapamil is specifically mentioned.
Q. Okay. And if we could now go back to page 4. I know I'm bouncing around a little bit. I'm sorry.
Do you see there's a table -- well, you will in a second -- there's a table on the right-hand side?
A. Yes, I'm familiar with that table.
Q. All right. And at the top, there are certain keys that tell you what a strong P-gp inhibitor is?
A. Yeah, that had two plus signs under -- there is an

inhibitor column all the way over on the right.

MR. MOSKOW: If you could make this bigger by just getting rid of the bottom third of that, Ms. Veldman, that would be great. Further down. Thank you.

Q. Do you see about halfway down here, we have carvedilol?

A. Yes.

Q. And then if we go across, it has those two pluses that are up here, strong inhibitor?

A. Yes.

Q. Is that information that you took into account when you were talking to the jury earlier about carvedilol and its interactions with Pradaxa?

A. Yes.

Q. And can you explain why?

A. Because just like the P-gp inhibitors mentioned in the labeling, this drug, which is not, would be expected to have the same interaction. So as a result, a patient needs to understand if they have severe renal impairment and are taking carvedilol, they would be at risk of blood levels that were too high.

MR. MOSKOW: Can we go to page 7, please.

And there are two take-home messages that I wanted to ask you about. The second one -- well, there were more than two. I just pulled out two.

Cardiovascular drugs with narrow therapeutic

indexes, antiarrhythmic agents, anticoagulant agents, can have large increases in concentration when coadministered with potent P-gp inhibitors, thus increasing the risk for drug toxicity.

Q. What does that mean with regard to Pradaxa and a strong P-gp inhibitor like Coreg or carvedilol?

A. So Pradaxa is an anticoagulation agent. So it's telling -- in this take-home message, it is saying if you have someone who is taking both Pradaxa, an anticoagulant, and taking a strong inhibitor, which we know that carvedilol is, that you're increasing the risk of toxicity. And we know that toxicity in this case is an increased risk of bleeding, and we know that bleeding is related to too much Pradaxa in the blood.

Q. And then the last thing on this paper I want to ask you about, this dose adjustment or use of alternative agents should be considered when strong P-gp mediated drug-drug interactions are present, what does that mean?

A. That means if you have a drug that you're taking, and you're taking one of these strong inhibitors, that you need to think about changing the dose of the drug or using a different drug altogether, the one that doesn't have this interaction as an issue.

Q. Are there anticoagulants that don't have this P-gp interaction as an issue?

A. There is others that have -- that will interact, but because of the way that they're absorbed to such a greater extent, it's not -- it doesn't drive it the same way.

So, no, this is one of those other unique issues with Pradaxa because it has such a low amount absorbed. Again, big effect with just a small change in the inhibitor. So that makes, to me, Pradaxa unique among the ones that are already on the market.

And one of the things I didn't say about the 2013 CCDS, there were other drugs like Pradaxa on the market then. So there were other alternatives that could have been used.

MR. MOSKOW: Okay. Take this down.

Let me try to get in one more document before -- I don't know when the Court wants to break.

THE COURT: When you're ready to have a break, we can take one.

MR. MOSKOW: I'm going to need to cut a little bit, so maybe do one document and then figure out when I'm going to cut.

THE COURT: Okay.

MR. MOSKOW: Thank you.

THE COURT: Do you want to break now?

MR. MOSKOW: I'd like to do one more before we break.

THE COURT: Go ahead.

BY MR. MOSKOW:

Q. Doctor, could you turn to page 80, please, Exhibit 80?

A. Middle, front?

Q. It's probably towards the front.

A. I see it, yeah. Okay.

Q. And what is Exhibit 80?

A. So this is essentially the labeling for Pradaxa in Europe.

Q. And specifically is this the labeling related to the 75-milligram dose?

A. Oh, yes. I'm sorry. Yes, it is.

MR. MOSKOW: Your Honor, I would move Exhibit 80 as a full exhibit.

MS. JONES: No objection.

THE COURT: It's admitted. It may be published.

MR. MOSKOW: Thank you, Your Honor.

(PLAINTIFFS' EXHIBIT 80 ADMITTED INTO EVIDENCE.)

Q. And it says S -- excuse me.

It says summary of product characteristics. Is this commonly abbreviated?

A. S as in Sam PC you'll see sometimes, yes.

Q. SMPC?

A. Yes.

Q. Okay. If we could turn to sage page 2.

Right at the very top, it tells us that this is Pradaxa

75-milligram hard capsule, right?
A. Yes.
MR. MOSKOW: All right. And if we go to page 3, what this is telling doctors in the European Union -- in all patients, it is about middle third of the page. Keep going. Stop there for now.
So in all renal patients -- excuse me.
In all patients, renal function should be assessed by calculating the creatinine clearance.
Q. Right, we already looked at that in the CCDS?
A. Yes.
Q. So this is -- this is not new information?
A. No. That's correct.
Q. And in Europe, doctors are specifically told that Pradaxa is contraindicated for patients with severe renal impairment, right?
A. That's correct.
Q. And then there's also talk about continuing to assess renal function when there is a decline suspected during treatment, right?
A. Yes.
Q. And it gives some examples why somebody might have a decline in treatment?
A. That's correct.
MR. MOSKOW: All right. And then in the interest of

time, we don't need to pull it up, but if you could get rid of the call-out. Just -- there you go. Great.

Q. Do you see that there is the information that we looked at earlier, the formula for calculating creatinine clearance?

A. Yes, that's correct.

Q. Okay. And it specifically says this method is recommended?

A. Yes, it does.

Q. Okay. If we could turn to page 5, please.

You see the section called haemorrhagic risk?

A. Yes.

Q. There's a section, the second paragraph, and once again it talks about factors that increase the levels of Pradaxa in the blood; is that right?

A. Yes, it is.

Q. And this is information that is communicated to doctors in Europe?

A. Yes, it is.

Q. And is this information important to you?

A. Yes.

Q. Why is that?

A. Because it is -- it is telling doctors in Europe that there is a relationship between these things, renal function changes and whatnot, and blood levels. And so it's giving

them information on what they can do to prevent that high level of exposure.

Q. Now are those instructions on how to prevent high levels of exposure important to you?

A. Yes.

Q. Why?

A. Because that is what is missing here. It's the idea that if you tell a patient and a physician that you can bleed, bleeding is dangerous, but you don't give them instructions or information on how to avoid that or identify people, it's a problem.

An analogy that I've used before is it's like you are driving down the road, and you see a sign blinking at you that says speed kills. But a little bit further down the road, you see a sign that says there's a speed grade, a curvy road. Those kinds of things give you more information about why you want to slow down and not just keep going rather than just telling you you can die if you speed. So those other signs give you a lot more information on how to factor how fast you should go.

So it's the same thing here. Doctors are being given information on what to do to identify those patients at greatest risk and to consider either a different dose, but also potentially alternative therapy.

Q. Based on your work in drugs and regulations regarding

drugs, what does this information reflect about Boehringer's knowledge of the risks associated with increasing Pradaxa levels in the blood?

A. It tells me that they understood not only that there was an increased risk, but also that they understood ways to modify that risk by identifying the plasma levels with those -- the presence of those kinds of conditions.

MR. MOSKOW: Great. Let's go to the last page. Excuse me, the next page.

Q. So do you see there is this chart at the top of page 6?

A. Yes.

Q. Is there important information here from your perspective reflecting what Boehringer knows about bleeding risks associated with this drug?

A. Yes.

Q. What is that?

A. It's putting together all of the factors in one place where you can go and pick them out. So it is showing you that you can increase plasma levels -- the second one down there. And it gives you the things that are important, which include renal impairment, co-medication with a P-gp inhibitor. It also talks about the fact above that, there is a separate factor for age.

And then the next one says here's another group of factors that are important to realize when you are talking

about using this drug. And that is you need to look at whether or not there's another drug, and they're listing aspirin -- ASA is aspirin -- that can also interact in another way.

So this is where you would be taking two drugs that both thin your blood, so that is a problem you'd have to worry about and consider as a doctor.

Q. I really wanted to ask you about diseases and procedures with special haemorrhagic risks. Do you see that?

A. Yes.

Q. And then there are a list of five bullet points right across.

A. Yes.

Q. The last one down, esophagitis, gastritis and gastroesophageal reflux, do you see that?

A. Yes.

Q. Where does, if at all, is that information in the patient Medication Guide for Pradaxa?

A. It's not there.

Q. Is that important information?

A. Yes.

Q. Why?

A. Because being what we know about the drug and the risk of bleeding in the GI tract, that puts these kinds of patients in particular at risk knowing what we know about

the drug.

MR. MOSKOW: And the last thing I want to do on this document before we break, just below this chart on page 6, there is a -- can you bring up the whole page, and I'll tell you what I want to pull out? The paragraph that says Pradaxa does not. Thank you.

All right. So there's a paragraph that says: Pradaxa does not in general require routine anticoagulant monitoring.

Let me stop there.

Q. Is that information that you are aware of before today?

A. Yes.

Q. And is that how the drug is marketed and sold in the United States?

A. As not requiring? Yes, absolutely.

Q. Do you take issue with this idea of routine anticoagulant monitoring?

A. I take issue on what that means versus what they could be doing. So to me, it's almost a semantic -- it's almost like hiding behind something that would be helpful because you don't want to do routine monitoring.

Q. Okay. What do you --

A. Do you want me to explain or --

Q. Yeah, please.

A. So warfarin is a drug that people have to go in week --

every several weeks or at least monthly and have your -- with a finger prick and have your blood tested to see whether you need to adjust the dose. So that is one of the disadvantages for some patients because it requires them to continually show up either at a doctor's office or at a facility where they can have that checked.

And the other issue with warfarin that some people have is they may have a hard time staying within that -- that range. But at least by checking the range, you're protecting the people from whether or not they have too much or too little of the drug in their blood. So it is a way to make the drug safer.

When this drug was developed, it was developed with the idea -- and documents that I've reviewed show this -- that they did not want to do monitoring. It's an advantage for Pradaxa, if they market it, to say no monitoring is needed. But the issue that I see with Pradaxa is we can make it safer not so much by doing routine monitoring, but by doing some monitoring. And that's the issue that I have with the drug, and I think that is the issue that they've actually put out there in some other internal documents, but they don't do it.

There is a way to make Pradaxa safer by doing some level of -- I wouldn't call it monitoring, I would call it blood level measurement at different times to make sure that the

the patient taking the drug is getting the right dose.
Q. When are those times that you think it should be done?
A. At initiation of therapy. So you put a new person on the drug, you wait until it -- four or five days or a week until the person has been taking the drug regularly to get to that steady state we talked about. You take a sample, and you monitor what their blood level is.

Based on that, you can compare that to what is known about the range and specifically the issue of what is too high and determine whether or not the patient needs to be on a different dose or a different medicine.

And that kind of assessment could be done -- let's say somebody didn't have kidney disease when they first started on Pradaxa. But two years later, due to their age, they now have severe renal impairment. It's another reason to consider measuring the drug and seeing whether or not it is still safe for that patient to use.

MR. MOSKOW: I want to read the next line and see if within the European label Boehringer acknowledges what you've just said.

However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors.

Q. Do you see that?

A. Yes.
Q. What does that say to you as a scientist working in this area?
A. It tells me essentially what I just said.
In other words, if you were to measure people's Pradaxa exposure, so excessive activities essentially saying how much Pradaxa is working in the blood, it could -- and people have a risk factor, you would be able to know whether or not you need to either change the dose or put somebody on a different drug because they're at risk.
Q. Where does it tell people in West Virginia in the patient Medication Guide that they can do this to avoid excessive exposure, to avoid too much Pradaxa?
A. There is nothing like that in the Medication Guide.
MR. MOSKOW: Your Honor, this is a good place to break.
THE COURT: All right. We'll take a 10-minute recess. You may retire to the jury room and sit down. We'll reconvene in about 10 minutes.
MR. MOSKOW: Thank you, Your Honor.
(Recess taken from 2:33 to 2:46 p.m.)
(Jury not present.)
THE COURT: All right. Ready to resume?
MR. MOSKOW: Yes, Your Honor.
THE COURT: Let's bring the jury out.

(Jury present.)

THE COURT: All right. Be seated.

You may resume your examination.

MR. MOSKOW: Thank you, Your Honor.

Q. When we just broke, Dr. Plunkett, we were looking at Exhibit 80, which is the European label.

Do you remember that?

A. Yes.

Q. We had looked at language that talked about detecting excessive dabigatran activity or excessive dabigatran exposure.

A. Yes.

Q. And, again, what does that mean simply?

A. Too much Pradaxa in your blood.

Q. Okay. And you talked about there were ways to do that with blood tests?

A. Yes.

Q. Did the company look at those ways to do that in the United States?

A. What do you mean by look at?

Q. Yeah, not a good question.

As you reviewed the company documents, did you see discussions among employees at Boehringer about whether it would make sense to test patients' blood to see whether they had too much Pradaxa?

A. Yes, they had discussions. I wasn't sure you meant that they did a study or had discussions. Yes, they did.

Q. And did some of those discussions look about how that testing would affect the sales of Pradaxa?

A. Yes, they did.

Q. Before we look at any more documents, let me ask you, based on your work in this area for more than 30 years, is it appropriate or inappropriate to look at sales when you're talking about patient safety?

A. To me, it's totally inappropriate. Patient safety should come first.

Q. Why is that?

A. Because that's what these drugs are being sold to do. They're not being sold to harm people. They're being sold to help people.

Q. If I could turn you to Exhibit 24 in your book.

What is Exhibit 24?

A. It's an e-mail string starting on March 16th, 2012, between several Boehringer employees.

MR. MOSKOW: Your Honor, I would move Exhibit 24 as a full exhibit.

MS. JONES: No objection, Your Honor.

(PLAINTIFFS' EXHIBIT 24 ADMITTED INTO EVIDENCE.)

MS. JONES: Could we be heard briefly at side bar?

THE COURT: Yes.

(Bench conference, reported.)

MS. JONES: I don't have an objection to the document, but I did just -- I have a sense where we're heading next in the examination, which is digging into the company e-mails. I did want to just flag for the record the guidance that the Court had given in its motion in limine order that there shouldn't be discussion with Dr. Plunkett about company motives or intent, et cetera, et cetera.

MR. MOSKOW: I'm trying to walk the line, Judge, of having her identify documents that fed into her opinions as to whether or not the company could and should do monitoring. So I am mindful of your order, and I'll do my best to walk the line.

THE COURT: Okay. I think that's fine.

MR. MOSKOW: Thank you.

MS. JONES: Thank you, Your Honor.

(Bench conference, concluded.)

THE COURT: All right. Go ahead.

MR. MOSKOW: Permission to publish, Your Honor, Exhibit 24?

THE COURT: Yes.

MR. MOSKOW: Thank you.

Q. Now, Dr. Plunkett, did you identify this document as one that you wanted to talk to the jury about?

A. Yes.

Q. Why was that?
A. Because it's addressing the issue of competition and disadvantages with the issue -- surrounding the issue of monitoring.
MR. MOSKOW: Okay. So let's pull up the bottom half of the document.
Q. And this is an e-mail from William Ragatz to Greg Behar and Christopher Kaplan, right?
A. Yes.
Q. And all of these e-mails reflect the U.S. division of Boehringer Ingelheim Pharmaceuticals?
A. That's correct.
Q. And was this document in the context of a larger discussion about blood tests?
In the prior pages in the document, were there other -- it is an e-mail, right, so e-mails go in different directions?
A. That's correct. In fact, there are -- yeah, there were ones that preceded, but they're redacted.
Q. Okay. We're not talking about those.
A. No. I'm starting with the one on the bottom.
Q. Okay. What I really wanted to focus you on is that this was part of a larger discussion.
A. Yes. And there's other e-mail chains with discussions around this same basic issue.

Q. Okay. The reason I asked that is because the first part of this says if we go down this route.

And could you tell the jury what you understood to be this route in the context of this larger discussion?

A. Plasma monitoring. Measuring levels of Pradaxa in blood.

Q. Okay. When you say plasma monitoring, are you talking about monitoring like with warfarin or something different?

A. Well, I believe it's something different than the monitoring for warfarin. It's the idea, though, of measuring blood levels of Pradaxa or anticoagulation activity in patients on Pradaxa and making decisions about whether or not the dose should be different or whether it's the right drug for the patient.

MR. MOSKOW: Okay. And so these folks at BI are talking about this.

And they say: First, if we go down this route, we will have to advise all patients to get some kind of anticoagulation monitoring, which would put us at a competitive disadvantage versus rivaroxaban or apixaban and force us to change part of our value story around not monitoring.

Q. What are rivaroxaban and apixaban?

A. So at this time in 2012, those were two other drugs that were competitors. They were also called NOACs, oral

anticoagulants. They were developed like Pradaxa to be as an alternative therapy to warfarin. And they're used in the exact same populations, generally the exact same populations. I don't know if they had all the indications for both of them by then, but they certainly were competitors in the atrial fibrillation market.

Q. And what is rivaroxaban?

A. Xarelto is the other name. People may have seen ads for Xarelto. And the other one is Eliquis, apixaban, which is another one that is advertised routinely.

Q. Okay. And do Eliquis and Xarelto have any kind of blood test to determine whether their levels are right?

A. They're not -- it's not required by the labeling, that is true. So it's -- none -- no three of these have that as a requirement by the labeling.

Q. So from your work in the industry, why would it put BI at a competitive disadvantage if they tested Pradaxa for excessive Pradaxa levels?

A. So unlike the other two drugs, Pradaxa had an advantage. They actually had collected a lot of data that allowed them to look at the relationship between blood levels and risk of bleeding and risk of stroke. The other two drugs didn't. So this is the drug where they actually had the data where they could make recommendations about plasma levels.

To me, that's an advantage, not a competitive

disadvantage. But they didn't want to have to monitor. That's the way the drug was developed. There's lots of other documents that talk about that was the goal of their development program, was to develop an oral anticoagulant as an alternative to warfarin that did not need monitoring.

Q. Was this something that you saw raised as a concern when that Reilly paper, that plasma concentration paper we looked at earlier, was being developed?

A. Yes. Before that paper was published, there were drafts, and the company went back and forth on what they should say in that paper and whether they should actually recommend a therapeutic range or not, stated specifically in the paper instead of having to go to that graph and extrapolate it down for yourself.

Q. Without pulling a lot of documents to show the jury, what did you understand the concern was of some of the folks at Boehringer as to whether stating a therapeutic range outright would be useful?

A. Many -- there were people that were involved in the development of Pradaxa, especially around the RE-LY trial, that thought this type of information, telling doctors about the relationship would be useful and actually make the drug safer. But there was also people within marketing and other parts of the company that did not want that message out. They wanted to maintain the message of no monitoring.

And if you put in a paper that there's a therapeutic range, that is admitting that there is a -- a range out there that would help doctors and could lead to the need for monitoring.

Q. Once you identify a therapeutic range, what are you telling the people at that P90 level?

A. You're telling them that you have too much, both ends. Essentially with that therapeutic range, if you were to say that's a range with P10 and P90, you're telling people that one in five, 20 percent out of 100, one in five of the people are not at the right level of Pradaxa in their blood, and they have a risk either of not having prevention of stroke or they are at a risk of bleeding. So it's a pretty big number, one in five people not at the right dose.

Q. Let's go to a different document.

Could you look at Exhibit 36 in your group there?

A. Yes.

Q. What is 36?

A. So it is another e-mail stream for people within the company that is around September -- it looks like between September and October, late September, early October of 2012. And they're talking about this issue of plasma blood levels and the RE-LY data.

MR. MOSKOW: Your Honor, I would move Exhibit 36 as the full exhibit.

MS. JONES: No objection, Your Honor.

THE COURT: It's admitted. It may be published.

MR. MOSKOW: Thank you, Your Honor.

(PLAINTIFFS' EXHIBIT 36 ADMITTED INTO EVIDENCE.)

MR. MOSKOW: Am I blocking the screen for anybody?

All right. And I want to start, if I could, at the top half of the first page. Actually that's all we're going to talk about.

Q. Do you see this is an e-mail from Dr. Clemens or Clemens at Boehringer to Dr. Friedman?

A. Yes.

Q. And you saw -- or you've reviewed the deposition testimony of Dr. Friedman that the jury saw yesterday?

A. Yes.

Q. And this is specifically referring to the concentration response paper, right?

A. Yes. This is that Reilly paper that eventually got published in 2014.

Q. So this is talking about earlier drafts of that paper?

A. Yes, that's correct.

MR. MOSKOW: And what I want to focus on is this point in the second paragraph.

The world is crying for this information, but the tricky part is that we have to tailor the messages smart. Thorsten wants to do that, so I think it would be worth it

if you and I would attend a TelCon for alignment. This I see as a real opportunity to not have a bad manuscript. Would be the last try to convince and guide Paul into an appropriate BI conform direction.

Q. Do you see that?

A. Yes.

Q. I want to start at the end of that sentence that says, to convince and guide Paul into an appropriate BI conform direction.

Based on your work as a scientist publishing peer-reviewed literature, reviewing that literature, does science have a company direction or is science science?

A. Well, science itself is science, and the data is what the data is. Certainly a company could have a goal, and they can try to achieve it. But making science fit your goal when it doesn't, that's not good science.

Q. And with regard to the plasma concentration paper, we saw Dr. Friedman tell the jury yesterday that there were earlier drafts that included a therapeutic range.

A. They did.

Q. How, if at all, does the change in that paper, where the therapeutic range was in and now was out when it was published, how, if at all, does that information inform your opinions as to whether Boehringer is fully disclosing the risks of Pradaxa to patients in West Virginia?

A. It's very important as part of my opinions. You want me to tell you how?

Q. Yes, please.

A. So the idea that you have a paper that appears in scientific literature and can use a term that people in the field would understand -- therapeutic range is an idea that a pharmacologist, someone working in clinical medicine would understand what that means.

If you understand it exists, and you don't tell physicians about it, but instead -- in fact, if you read that paper, they try to twist that message around in a different way based on what was in the earlier manuscript -- to me is wrong.

I mean, the idea is the drug can be safer, and this is -- this paper in the early drafts when it used the word therapeutic range had a way to make the drug safer for some people. And so I think hiding that information by taking it out of the draft is wrong and is not putting the best science forward.

Q. This -- I want to touch on two last things on this.

The point that the world is crying for this information, is that a statement you agree with?

A. Yes.

Q. Why?

A. Because up to this time, in other documents that I've

seen that relate to this conversation within the company, it was pointed out by some other clinicians who were working on this paper that it would be very helpful for doctors to understand how to pick the right dose and the right drug for their patients. And that's what this information on therapeutic range would do. It would tell you, based on having gathered this data, here's a way we can use it, and this is a way you can know that your patient on Pradaxa is not one of those patients that has risk factors based on who they are that put them at excessive risk of bleeding. So it's the idea of making the drug safer for the patients that you give it to.

Q. This is October of 2012, right?

A. Yes.

Q. I want to take you back very quickly to Exhibit 5, which is about a year and a little bit earlier.

A. Okay.

Q. And are you able to identify Exhibit 5?

A. Yes.

Q. What is that?

A. It's another group of e-mails dated August 1st, 2011, between Dr. Reilly and some other scientists in the company.

Q. Okay. And does this deal with that same plasma concentration paper?

A. Yes. It's called the PK outcomes paper, but also called

in the other e-mail exposure response. But it's the paper that Dr. Reilly was working on.

MR. MOSKOW: Your Honor, I would move Exhibit 5 as a full exhibit.

MS. JONES: No objection.

THE COURT: It's admitted and may be published.

MR. MOSKOW: Thank you, Your Honor.

(PLAINTIFFS' EXHIBIT 5 ADMITTED INTO EVIDENCE.)

MR. MOSKOW: So I want to stay on the first page of this. We are going to move very quickly. But the bottom half of the page is an e-mail at 16:46 on Monday, August 1st.

Q. Do you see that?

A. Yes.

Q. And there's some German on this document.

Do you know if Dr. Brueckmann, Professor Dr. Martina Brueckmann is in the German department of Boehringer Ingelheim?

A. Yes, in medical affairs.

Q. In fact, the DE in her e-mail indicates that she's in Deutschland or Germany, right?

A. And Dr. Reilly, you'll see U.S. with his.

Q. Okay. And can you read this e-mail to the jury?

A. Dear Martina: Of course I am aware that the conclusions that appear to emerge from this paper are not the ones

currently wished for by marketing (that dose adjustment will optimize therapy). Let's just see where this paper ends up. I actually think that once we have a competitor out there that is as good as we are, we will be looking for ways to make our drug better. Ultimately, if BI doesn't want to be associated with this message, I recognize that BI authorship may not be possible.

Q. Again, based on your experience, does marketing drive science?

MS. JONES: Excuse me, Dr. Plunkett.

Your Honor, I am going to object in light of Your Honor's motion in limine I raised at side bar.

THE COURT: Sustained.

MR. MOSKOW: Let me rephrase the question.

THE COURT: Okay.

BY MR. MOSKOW:

Q. Doctor, based on your work in the regulatory and scientific fields, how do you view marketing's role in the progress of science?

MS. JONES: Your Honor, I'm going to make the same objection.

THE COURT: Overruled.

THE WITNESS: Marketing, in my experience, is not supposed to play a role in how the science evolves and develops. Again, marketing can be involved in an initial

goal. This is a good market to go into. This is the type of drug that would be useful. But once you start to gather the science and the data, marketing should not be driving the information that gets to physicians.

MR. MOSKOW: If we could go to the e-mail at the top half of the page, please.

Q. Dr. Brueckmann responds to Dr. Reilly later that same day?

A. Yes.

Q. And she writes: Fully agree. A target range is something we always wanted to avoid in the first place to get away from monitoring.

Right?

A. Yes.

Q. And based on your review of the documentation, is that a consistent company position?

A. Yes, absolutely.

Q. She goes on to say, the fourth line down: The time may be a bit too early to introduce a target plasma level range from a marketing point of view. But if this could clearly demonstrate that additional benefits are obtained, this may be a path forward to differentiate ourselves from competitors.

Do you see that?

A. Yes.

Q. Based on your experience working in this field, is patient safety something that waits until you have a competitor, or do you address it immediately?

A. It should be addressed immediately. And that's really what is meant to happen by the way the process goes about. That is sort of the way the regulations talk about protecting patient safety. That's what is supposed to happen.

Q. If we could go to Exhibit 38, please, in your book.

A. 38. Okay.

Q. And what is that?

A. It's -- the first -- it is an e-mail stream. If you want the first one, it's dated June 24th, 2012.

Q. Are you at 38?

A. Oh, I'm sorry. Wrong one.

38, an e-mail stream, but this date is February 4th, 2013, and it's talking about the exposure paper again, so Reilly's publication that eventually comes out.

MR. MOSKOW: Your Honor, I move Exhibit 38 as a full exhibit.

MS. JONES: No objection.

THE COURT: It's admitted, and it may be published.

(PLAINTIFFS' EXHIBIT 38 ADMITTED INTO EVIDENCE.)

MR. MOSKOW: All right. So let's take the first half of the page, the first page, please.

THE WITNESS: Sure.

MR. MOSKOW: And this is an e-mail from Dr. Jutta Heinrich Nols.

Q. Do you see that at the top?

A. Yes.

Q. And she's writing to Dr. Friedman, Dr. Brueckmann, and Dr. Clemens.

A. Yes.

Q. Based on your review of documents and information at Boehringer, are these senior or junior people in the development of Pradaxa?

A. These are people -- decision-makers, senior people.

Q. Okay.

MR. MOSKOW: And Dr. Heinrich Nols writes:

Dear all, is it really wanted to publish this exposure event paper of RE-LY? I cannot believe that for a decade a drug was developed with a clearly defined target of no monitoring needs, a prospective trial without plasma level monitoring was performed generating the RE-LY study results that we promote two fixed doses without monitoring, defend continuously to health authorities that individual patient characteristics do not allow a dose titration based on plasma level only, and then finally release a publication where exposure event relationships, which was neither prospectively defined nor adequately conducted, are

described to define an effective and safe plasma level range. This will make any defense of no monitoring to HA extremely difficult, i.e. Health Canada and TGA, and undermine our efforts to compete with other NOACs.

Let me stop there.

Q. Can you explain to the jury what this will make any defense of no monitoring to HA extremely difficult means?

A. It means that if health authorities are actually asking questions about the need to monitor, it will be very hard to say we don't need to monitor if they put this paper out, which actually identifies a useful therapeutic range for doing such blood level assessment or measuring levels of Pradaxa in blood and relating it to risk.

Q. Okay. Earlier when we were looking at another e-mail, you said that it was always appropriate to have a target of no monitoring.

Do you disagree with that?

A. No, absolutely not.

Q. So what's the problem with monitoring now?

A. Because you actually know that it could be helpful and would make the drug safer. I mean, there again, other discussions within e-mails that I have seen and in company documents where they recognize that they could have a safer drug.

I mean, that is what they are talking about in the one

we just did. Make the drug better? Making it better means making it safer in this case when you can identify patients at risk.

So, again, no problem with them having a goal of no monitoring. But when they collect the data -- they collected a large amount of data that was extremely useful. To ignore what that data tells you, especially for vulnerable people like the ones with severe kidney impairment on multiple drugs, that's a real problem in my view. I don't think that that is consistent with protecting patients.

Q. All right. I want to end my time with you -- I know Attorney Jones will have some questions for you, but I want to end my time with you looking at Exhibit 93.

A. Okay.

Q. What is Exhibit 93?

A. It's the -- sorry -- the labeling that is written for the doctors. So it's for the prescribers for Pradaxa. And this looks like it is -- look at the date -- 2013, April of 2013.

Q. I don't mean to correct you, but is this the labeling just for doctors or does it include information specifically for patients?

A. Well, the front page is the labeling for doctors. But you're exactly right, at the back there is a Medication

Guide. So this is the full labeling for the drug.

MR. MOSKOW: I move Exhibit 93 as a full exhibit.

MS. JONES: No objection, Your Honor.

THE COURT: It's admitted and may be published.

MR. MOSKOW: Thank you.

(PLAINTIFFS' EXHIBIT 93 ADMITTED INTO EVIDENCE.)

BY MR. MOSKOW:

Q. Let me just ask you generally, when you talk about the label, what are you talking about? Are you talking about the thing that is on the bottle?

A. Well, that is actually part of it, but the labeling is more than that. For a prescription drug, there's a lot of things that make up the label. The thing that is on the bottle is regulated as part of the label. The Medication Guide that is handed out to the patients, that's part of the labeling. The larger, more detailed instructions that are given -- made available to doctors is labeling. And even promotional materials, advertisements that you see on the TV and things like that, those are considered part of labeling for the product.

And that means that all of that has oversight, and all of that has certain ways that it's supposed to be developed and produced and made available to doctors and then also to patients, in this case with the Medication Guide.

Q. Okay. So you said in patients in this case with the

Medication Guide.

Why is there separate information for patients with regard to Pradaxa?

A. So it's understood that the language in the label for the doctors is going to be way too detailed, but also there are a lot of terms and a lot of language that won't be known by the average person. So rather than requiring you to have a medical degree or a doctorate in order to understand the label or a science degree of some kind, they make a shorter more concise version of important information that is drafted in language so the average person could understand it and read it. And then it either may lead to opening a dialogue with your doctor, or it may just be with your pharmacist, or it may be that you just have it at home, and you read it and understand it.

Q. Is this done for all drugs?

A. No.

Q. Why not?

A. Because many drugs don't have the kind of serious risk issues or concerns that require there to be specific information given to patients.

I see this kind of Medication Guide for all anticoagulant -- all anticoagulants have one. I see it for -- a drug like Accutane has one because of the risks to being pregnant if you're taking that drug.

So the drugs that have these more serious patient safety concerns or more serious issues of how to take the drug, those are the ones that will have a Medication Guide.

Q. How is it that Pradaxa came to have a Medication Guide?

A. Because of the type of drug it is.

I know Mrs. Kliewer mentioned in her depo that it wasn't a regulatory requirement. That's true, it's not. But it is one that is often recommended and asked for by the agency. And certainly I think it's appropriate for this kind of a drug being it is one that you need to understand the risks.

Q. Do you have an understanding of whether part of the labeling negotiations for Pradaxa included a need to have a patient Medication Guide?

A. Yes, that was mentioned during the labeling negotiation.

Q. All right. And then the last thing I wanted to ask you before we actually get into the nitty-gritty here, have you seen any studies anywhere that talk about how drug safety can be improved by the delivery of warnings and instructions directly to patients?

A. Yes.

Q. And generally speaking, what do you understand about that?

A. That very specific targeted information in plain language is able -- when given to patients outside of not being given to patients when they do studies, they see that

it improves the safe use of the drug. That patients have a better understanding, and with a good Medication Guide, that there's actually a lower incidence of certain kinds of adverse events and things like that because people understand it better.

MR. MOSKOW: Let's turn to page 12 of Exhibit 93. And if you could take out the first half of the label -- yeah, through the second point. Thank you.

Q. So this is the very beginning of the Medication Guide, right?

A. Yes.

Q. And patients are told to read this before you take it and to read it each time you get your new medication?

A. Yes.

Q. And that's important because why?

A. Because the information can change. It is the idea that each time you get a refill, it's possible that the labeling has changed, and so there could be new information that would be useful that you need to understand and that your doctor hopefully will open up a dialogue with you as well.

Q. Then the first section is what is the most important information I should know about Pradaxa, right?

A. Yes.

Q. And in the interest of time, I won't make you read everything. But this first paragraph is really talking

about why you take Pradaxa, right?
A. That's exactly right.
Q. And it is important to take an anticoagulant if you have AFib and your doctor prescribes it; is that fair?
A. Yes, absolutely.
Q. Can you tell the jury why?
A. Because indeed, as Dr. Friedman described when I saw his depo, you're at an increased risk of blood clots, and those block clots can lead to various serious strokes. So if you can prevent those from happening because your heart is not beating properly, then this kind of drug is very useful and has been shown to be effective.

So, yes, it's important to realize if you have an ongoing condition of atrial fibrillation that is not being able to be treated properly, then an anticoagulant is definitely important.

Q. Now the only thing bolded in this section is that you should not stop taking Pradaxa without talking to the doctor who prescribes it for you, correct?
A. Yes.
Q. Why?
A. Well, as soon as you stop, you're at an increased risk of a stroke. They have actually data that shows that the risk is higher if you promptly stop than if you don't.
Q. But then the next section says you may need to stop it

if you are going to have surgery.

A. Yes.

Q. Can you explain to the jury that balance of stroke risk versus bleed risk that is being discussed here?

A. Right. So you take the drug because you want to prevent a stroke. But if you're going to have surgery, and you're going to bleed because they're cutting into your tissues, if you're on this anticoagulant, you could just not ever clot, and you could actually die from excess bleeding due to the surgery.

So, as a result, if you go into your doctor, and he wants to do any kind of procedure like a colonoscopy or even some types of dental procedures, you're required to stop -- they tell you to stop taking the drug before you have that done so that you don't have that risk of a life-threatening bleed or even just really excessive blood loss that could require you to be hospitalized in order to replace the blood.

Q. And then the next bullet point is the warning that you talked about before, Pradaxa can cause bleeding which can be serious and sometimes lead to death, right?

A. Yes.

Q. And I think you used an analogy about a sign on the highway that says speed kills?

A. Yes.

Q. Why did you use that analogy to talk about this language?

A. Because this language is telling you that -- something about the fact that bleeding can -- bleeding can kill you, but it is not providing in this Medication Guide information about how to avoid that risk. How to put those things together to understand -- in other words, the idea that telling a person on a 75-milligram dose that, oh, by the way the drug hasn't been tested or -- for you, shown to be safe and effective.

Or if you're bleeding, and you have these risk factors, those things could all combine together to make it so that if you're old, and you have severe renal impairment, and you are on a strong P-gp inhibitor, you are really at an increased risk of bleed.

So it's providing context so the patient understands that bleeding is a risk, but there is ways that I can -- this drug can be safer for me. Measuring the blood level is an example of something that could be provided to the patient or mentioned to the patient as well.

Q. What opinion, if any, do you have as to whether simply warning a patient that Pradaxa can cause bleeding which can be serious, and sometimes lead to death, is an adequate warning?

A. It's my opinion that it's not adequate based on a lot of

other information that is known that would help them prevent or avoid that bleeding risk.

Q. I want to stop for a second while this is on the screen and just ask you, do you, as part of your consulting practice, advise clients as to the types of warning instructions they need to give to doctors and patients?

A. I have, yes.

Q. And when you do that, what significance is there, if any, as to how individual state laws may apply versus FDA rules?

A. So I've worked on projects or cases where the issue is whether or not the information needs to be provided directly to a patient -- like in this case, that's my understanding here in West Virginia -- versus the information only having to be provided to the physician.

So in some projects that I work on what is most important is what is being told to the patient, and that's what this Medication Guide is. So in my view that is what is really important in this particular case, understanding what the patient was being told.

Q. Let's look at the bottom half of this page of the Medication Guide.

It says: You may have a higher risk of bleeding if you take Pradaxa and -- and it lists a bunch of things, right?

A. Yes.

Q. Age over 75 years?
A. Yes.
Q. Kidney problems?
A. Yes.
Q. If you're on other medications?
A. Yes.
Q. If you've had stomach or intestine bleeding that is recent, and it keeps coming back?
A. Yes.
Q. I mean, this is a whole bunch of medications here, right? I mean, we can count them up, but there are a whole bunch of medications that are listed here.
A. Yes.
Q. Do you have an opinion as to whether this is adequate information to patients?
A. I do.
Q. And what is that opinion?
A. That it's not.
Q. Why is that?
A. Well, there's a couple of issues. One -- on the issue of medications, there are other drugs out there that are strong P-gp inhibitors that are commonly used with this drug that I believe should be discussed or described or at least they should be told to ask questions about with their doctor.

And then there's this issue of pointing out that -- on this issue of higher risk of bleeding, the idea that multiple risk factors puts you at even greater risk. It's the idea that you may -- you have to understand, if you have three or four of these things, it's a real problem. And there is a way to find out if the drug safe for you, however, with those factors. And that's the issue of plasma -- monitoring the level of Pradaxa in your blood.

MR. MOSKOW: In the interest of time, let me see if I can walk you through the Medication Guide as a whole.

Gina, can you just flip through pages 12 to 16 very quickly and just show the four pages or maybe put all four of them up at one time?

Q. Okay. So this is a four-page document with big print, right?

A. Yes.

Q. And we'll put the first two pages up.

Have you had an opportunity to review the entire Medication Guide?

A. Yes.

Q. Okay. So I'm going to ask you a series of questions, and I'm going to ask you to identify, and then Ms. Veldman can pull up on the screen the area you're talking about.

All right?

A. Sure.

Q. Can you direct Ms. Veldman to put up on the screen where in the Medication Guide it says that the 75-milligram dose was never tested on AFib patients?
A. That is not in the Medication Guide. The patient would have no way to know that.
Q. Okay. Could you tell us where we're going to find that there is no safety and effectiveness information about the 75-milligram dose?
A. That is not in there.
Q. Can you show us where there is information that one in five patients are getting too much or too little drug?
A. That is not in there.
Q. Can you point where in the Medication Guide it talks about excessive dabigatran exposure or too much Pradaxa?
A. That concept is not provided in here.
Q. Can you point to where in this label it tells us that too much Pradaxa increases your risk of bleeding?
A. It doesn't use those words.
Q. Where does it say that increasing plasma -- increasing plasma concentration increases the risk of bleeding?
A. It does not mention that relationship.
Q. Can you show the jury where in this label it says that if you're on Pradaxa, you're more likely to have a GI bleed -- strike that. Let me start again.
Tell the jury where in this Medication Guide it tells a

patient that you are more likely to have a GI bleed with Pradaxa than you would with warfarin?

A. It doesn't provide that data.

Q. Where in this Medication Guide does it tell a patient that there is no reversal agent, there is no way to stop an active bleed?

A. It also doesn't provide that information to the patient.

Q. Where in this label -- strike that.

Where in this Medication Guide does it identify the strong P-gp inhibitor Coreg or carvedilol should not be used with somebody who has severe renal impairment or significant kidney problems?

A. It does not mention that together.

Q. And I think you already said this, but can you point anywhere in the label where it says -- strike that.

Can you point to anywhere in this Medication Guide where it says that if you add risk factors, the risk of bleeding is increased more than just one plus one plus one?

A. It doesn't provide that information.

Q. Have all of the opinions that you've given this jury over the course of the entire day been given to a reasonable degree of scientific and regulatory certainty?

A. Yes, they are.

Q. And just to confirm one more time, what does that mean to you?

A. That is the more likely than not standard. I believe that the information I reviewed and relied upon shows that it's more likely than not that those opinions I have expressed are true.

MR. MOSKOW: Your Honor, may I have one moment?

THE COURT: You may.

(Plaintiffs' counsel conferring.)

MR. MOSKOW: Your Honor, I'm going to tender the witness.

THE COURT: All right. We'll take a brief recess before cross-examination begins. You may retire to the jury room.

MR. MOSKOW: Thank you, Dr. Plunkett.

(Recess taken from 3:28 to 3:35 p.m.)

(Jury not present.)

THE COURT: All right. Ask the jury if they're ready. They can come out when they're all ready.

THE COURT SECURITY OFFICER: Yes, sir.

MS. JONES: And, Your Honor, I obviously have more than I'm going to cover this afternoon, so I'll stop at a reasonable breaking point if that makes sense for Your Honor.

THE COURT: Absolutely.

(Jury present.)

THE COURT: All right. Be seated.

MS. JONES: Thank you, Your Honor.

CROSS-EXAMINATION

BY MS. JONES:

Q. Good afternoon, Dr. Plunkett.

A. Good afternoon.

Q. I don't think we've ever formally met. I am Phyllis Jones. I am one of the lawyers for BI. It's nice to meet you.

How are you doing?

A. I'm fine, thank you. And I don't think we have met. Nice to meet you.

Q. Likewise.

So we don't have as much time as I will need to finish your cross-examination, so I may jump around a little bit to try to get into some things that we can finish in an efficient way if that's okay. All right?

A. That's fine.

Q. All right. I actually want to start where you ended up with Mr. Moskow in talking about the Medication Guide for Pradaxa. Okay?

A. Okay.

Q. Do you have Exhibit 93 in front of you?

A. Yes, I do.

MS. JONES: And can we pull that up on the screen, Mr. Reynolds? And let's just go to start to page 12 of

Exhibit 93.

Q. And just to remind ourselves, this is a copy of a version of the Pradaxa label from April of 2013; is that correct?

A. Yes.

Q. And what we're looking at towards the back of the document is what you described as the Medication Guide, correct?

A. Yes.

Q. And the Medication Guide is a document that is prepared specifically for patients, correct?

A. Yes.

Q. And by the rules that are established by the FDA, every time that a patient goes to a pharmacy to pick up a prescription for Pradaxa, that patient is supposed to receive a copy of the Medication Guide, correct?

A. Yes, that is correct.

Q. All right. And just to be clear, following up on what you were covering with Mr. Moskow, the Medication Guide for Pradaxa is not the only resource that is available that contains information about the benefits and the risks of Pradaxa, correct?

A. Are you meaning just to the patient only or are you saying just generally?

Q. I'm saying generally.

A. That's true. Generally there is other information.
Q. Okay. And in fact, if we look at the very beginning of Exhibit 93, we see what I think you referred to as the physician labeling for Pradaxa, correct?
A. Yes.
Q. Okay. So let's start back with the Medication Guide, and then we will probably flip back to the beginning of the document at least briefly.
At the very top of the Medication Guide for Pradaxa, there is actually just some advice to patients about how to use the Medication Guide, correct?
A. Yes.
MS. JONES: And can we call out that first paragraph, Mr. Reynolds?
It says: Read this Medication Guide before you start taking Pradaxa and each time you get a refill.
Q. Did I read that correctly?
A. You did, yes.
Q. And you don't take issue with that suggestion to patients, correct?
A. No.
Q. That's good advice, right?
A. Yes.
Q. Okay. And it goes on to say there may be new information. That's the reason that a patient might want to

read it each time he or she receives it, correct?
A. Yes.
Q. It goes on to say: This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.
Correct?
A. Yes.
Q. So the Medication Guide, I think this was something that you referenced in your direct testimony, also is intended to encourage a conversation with the patient's doctor, correct?
A. Yes.
Q. And that makes sense because Pradaxa is a prescription medicine, correct?
A. That's correct.
Q. You can't get Pradaxa unless a doctor or some health care professional who is authorized to prescribe medicines says you should have this medicine, correct?
A. That's correct.
Q. Okay. And so you don't take issue, I assume, with this advice in the Medication Guide that says this doesn't take the place of talking with your doctor about the medicine, correct?
A. I have not had issue with that, no.
Q. Okay. And am I right in understanding that every single word of this Medication Guide for Pradaxa has been approved

by the Food and Drug Administration?
A. Yes, that's correct.
Q. And if we actually go to the very last page of the Medication Guide, you see there is a reference there -- it's about a fifth of the way down the page, Mr. Reynolds -- where it says this Medication Guide has been approved by the U.S. Food and Drug Administration?
A. That's correct.
Q. All right. And so that just confirms that every piece of content that appears in this Medication Guide for patients, the FDA gave it its seal of approval, correct?
A. That's what is supposed to happen, yes, and I believe it did in this case.
Q. All right. Then if we go to page 15 of Exhibit 93, just moving further back into the Medication Guide, it also says -- there's a section at the bottom that says General Information About Pradaxa, correct?
A. Yes.
Q. And it says -- I want to go actually to just that middle paragraph. It says: This Medication Guide summarizes the most important information about Pradaxa.
Correct?
A. Yes.
Q. And you don't take issue with that reference in the document, correct?

A. To the reference? No.
Q. Okay.
A. No.
Q. It goes on to say: If you would like more information, talk with your doctor.
Correct?
A. It does say that, yes.
Q. And that's good advice, correct?
A. Yes.
Q. You don't have any issues with that language in the Medication Guide, correct?
A. No, I have not commented on that.
Q. Okay. And it goes on to say: You can ask your pharmacist or doctor for information about Pradaxa that is written for health professionals.
Do you see that?
A. Yes.
Q. And do you understand that to be a reference to the physician labeling that is also made available by Boehringer Ingelheim to doctors and health care professionals who actually prescribe Pradaxa?
A. Yes, that's my understanding.
Q. Okay. And you covered a lot during your direct examination testimony today, but you did not cover at all, if I'm recalling correctly, any of the detail in the

labeling for physicians for Pradaxa; is that right?
A. We did with -- I don't believe in the U.S. label. We did go into the European label, which was for physicians.
Q. Got it. And that's a fair clarification.
You talked about the label that doesn't apply in the United States, but you did not talk about the doctor label that would apply in the United States, right?
A. That's correct. It's my opinion the Medication Guide is what is relevant.
Q. Okay. But we can agree, because we just looked at it, that the Medication Guide also encourages patients to talk to their doctors who have access to the physician labeling, correct?
A. It does say that, that's true.
Q. Okay. And do you understand there to be --
MS. JONES: I apologize. I apologize to everyone. That's a failing of mine. I will try to do better.
Q. Do you understand there to be something that is the equivalent of the Medication Guide in Europe?
A. Yes.
Q. Have you looked at that?
A. I've seen something that was available online, yes.
Q. Did you evaluate it to determine whether you viewed it as adequate or not?
A. No. I haven't made an opinion on any specific language,

no.

MS. JONES: Could we just go to the first page of Exhibit 93, Mr. Reynolds?

Q. And there is more in this document to cover than we're going to be able to cover this afternoon, but I just wanted to give a little bit of a quick run through of some of the highlights in the document. Okay?

A. Okay.

Q. So on the first page of Exhibit 93, we are looking at what's known as the highlights section for the prescribing information for doctors and medical professionals who prescribe Pradaxa, correct?

A. Yes, that's correct.

Q. And this is information that is given to health care professionals so that they can provide whatever information they think is appropriate for their patients, correct?

A. Yes.

Q. Okay. And this is the type of information that the Medication Guide is envisioning when it says talk to your doctor, your doctor can give you the information that is made available for health care professionals, correct?

A. Well, I wouldn't think they were only talking about the highlights, but certainly the information generally I would agree.

Q. And, again, that's a fair clarification. I was

referencing the doctor label in general.
A. Okay. I'm sorry. I thought we were just talking about the highlights, but that's fine.
Q. We're on the same page.
The doctor label is what the Medication Guide is referring to when it says talk to your doctor, your doctor might be able to give you more information including the labeling for doctors, correct?
A. Yes, that's true.
Q. Okay. And if we just call out that top section -- thank you, Mr. Reynolds -- this, again, is a section that is regulated and approved by the FDA, correct?
A. Yes, that's correct. This is part of that labeling negotiation process in the beginning and then also later.
Q. And then the structure of a doctor label for a medicine, that is all regulated by the FDA as well, correct?
A. Yes. There are a certain part of the regulations that tell you how to -- what sections need to be there and how to put it together, yes.
Q. And so a company like BI couldn't say we want to name the sections differently or we want to somehow switch up the organization of the sections, correct?
A. That is true, no.
Q. Okay. And if the FDA says we don't want something in the label, the company cannot then say, well, we're going to

put it in there anyway, correct?
A. It can push back. But if the FDA has made a final decision it's not to be there, then they are to -- they're supposed to follow the FDA's advice, that is true.
Q. Okay. And in the Highlights of Prescribing Information, this is a little bit of a summary of all of the information that is captured for doctors in the labeling for physicians, correct?
A. I wouldn't put it quite that way.
Q. How would you put it?
A. I would say this highlights is the most important information about safety and effectiveness that is in there, because there is not as much information on clinical pharmacology and those other sections here.
Q. I like your definition. I'm good with that definition.
So just to run through some of the areas that are covered here, if we start just by looking at Indications and Usage, that is the section that just talks about what is the medicine used for and how do you use it, correct?
A. Yes.
Q. Okay. And then there's another section that is entitled Dosage and Administration, correct?
A. Yes.
Q. And it specifically identifies the two dosages of Pradaxa that are available for patients, correct?

A. Yes.
Q. And it explains how you decide how to dose Pradaxa based on a patient's kidney function, correct?
A. It mentions it in the third bullet. If that's what you're asking me, yes.
Q. Actually I was referring to the first and the second bullet.
A. Oh, I'm sorry. You mean the creatinine clearance levels? Yes, those are listed.
Q. Okay. Then in the third bullet -- you were anticipating where I was going next -- it tells doctors: Assess renal function during therapy as clinically indicated and adjust therapy accordingly.
Correct?
A. Yes.
Q. All right. And you can see behind some of those instructions to doctors that there are numerical references, correct?
A. Yes.
Q. And those are -- those are numbers that actually refer to specific sections in the label, correct?
A. Yes.
Q. And so if a doctor just looked at the highlights of the -- of the label, they would be able to see pretty quickly this is the section I need to look in to find more

information on this topic. Is that fair to say?
A. Yes.
Q. Okay. Moving on to some of the other sections on this same page, there is a section called Contraindications, correct?
A. Yes.
Q. And those are -- those are particular patient characteristics where the company and the FDA determined these folks should not be on the medicine, correct?
A. Yes.
Q. Okay. And then in the next section, there's something titled Warnings and Precautions, correct?
A. Yes.
Q. And that is the place where you probably find the most serious safety information about the medicine, correct?
A. Yes.
Q. Okay. And the very first warning and precaution that appears in the highlights section for Pradaxa reads: Risk of bleeding, Pradaxa can cause serious and sometimes fatal bleeding. Promptly evaluate signs and symptoms of blood loss.
Correct?
A. Yes.
Q. And so a doctor who did nothing more than just reading the first page of the label for Pradaxa would know this is a

medicine that can cause serious and sometimes fatal bleeding, correct?

A. Yes.

Q. And if we looked at the labeling for all of the other oral anticoagulants that are available for patients who have atrial fibrillation, those labels would have very similar warnings, correct?

A. In fact, they do, yes.

Q. They do have similar.

In some cases, they're identical I think for the NOAC medicines; is that right?

A. Yes, that's correct.

Q. Okay. And so that's not a risk that is unique to Pradaxa, correct?

A. The bleeding risk?

Q. Yes.

A. Yes, that's true.

Q. At the end of that list of items under Warnings and Precautions, you see there is a reference there to P-gp inducers and inhibitors. Do you see that?

A. Yes.

Q. And then it says: Effects on dabigatran exposure. Do you see that?

A. Yes.

Q. And you mentioned earlier that there was nothing in the

patient Medication Guide on the subject of P-gp inhibitors. But you understand that there is information in the package insert for Pradaxa for doctors that talks about P-gp inhibitor medicines, correct?

A. There is some information there, yes.

Q. Okay. And then the next section in the highlights for the labeling for Pradaxa is entitled Adverse Reactions. Do you see that?

A. Yes.

Q. And it says: The most common adverse reactions, and then it just refers to those being greater than 15 percent -- are gastritis like symptoms and bleeding. Do you see that?

A. Yes.

Q. Okay. And then there's a section for drug interactions. Do you see that?

A. Yes.

Q. And at the end of that list -- actually all of those -- all of those bullets refer to either P-gp inhibitors, which are one class of medicines, correct?

A. Yes, they are.

Q. Or there's a reference to something known as P-gp inducers, which are different types of medicines, correct?

A. Yes. They do different things to the blood levels.

Q. And then at the bottom of that list of drug

interactions, it reads: P-gp inhibitors in patients with severe renal impairment, creatinine clearance less than 30 millimeters per minute, Pradaxa use not recommended.

Do you see that?

A. Yes.

Q. Okay. And so you understand that the labeling for doctors for Pradaxa actually does provide guidance to doctors on patients who have severe rental impairment and might be on a P-gp inhibitor, correct?

A. They have some information, yes.

Q. Okay. Well, not just some information.

They specifically say we don't recommend it necessarily in these patients, correct?

A. Yes. Well, I have issues with some of the details when you go back to the label, but -- that part of the label, but I agree there's a general statement here, that is true.

Q. That it is not recommended, correct?

A. That is what -- yes, you read that in correctly.

Q. Okay. And then the last reference there is to use in specific populations. Do you see that?

A. Yes.

Q. And then it says: Geriatric use, colon, risk of bleeding increases with age.

Do you see that?

A. Yes.

Q. And that's a true statement, correct?
A. Yes.
Q. As folks get older, as we all get older, our risk of having a bleed increases, correct?
A. That's correct.
Q. And then down at the bottom of the first -- that first page of the Pradaxa label, there is a table of contents or index that goes through each of the sections in the labeling, correct?
A. Yes, that's correct.
Q. And so if we just look quickly, there's a section for indications and usage. Yes?
A. Yes. This is what those numbers above refer to.
Q. They correspond to what we just went through, right?
A. That's correct.
Q. And there are also references there for clinical pharmacology, which is your area of expertise, correct, as well?
A. Yes.
Q. And there's a section for toxicology, for example, correct?
A. Yes.
Q. A section about clinical studies on the medicine, correct?
A. Yes.

Q. And then there's a section on patient counseling, giving doctors advice on how they counsel -- they might counsel their patients who are on Pradaxa, correct?
A. Yes.
Q. Okay. And we don't have time to go through all of this this afternoon, so I'm not going to try. But when we go through it tomorrow, some of those things that you saw on that wheely board over there, some of those specific issues are raised in the physician labeling for Pradaxa, correct?
A. If by you mean raised [sic], there is some discussion somewhere in the labels for some of those, that is true.
Q. Well, for example, does the physician labeling for Pradaxa specifically say there is not a reversal agent for Pradaxa? Yes or no?
A. The physician? Yes, it does.
Q. All right. Let me ask you just a little bit about this particular case.
Did you know that you were the first live witness we've had come to see us?
A. I was told that, yes.
Q. Okay. All right. And you understand that this case is about a specific person who took Pradaxa, correct?
A. Yes.
Q. Do you know the name of that person?
A. I know her name was Mrs. Knight. I believe Betty may

have been her first name.
Q. Okay. Have you reviewed any of the medical records for Mrs. Knight?
A. No, I have not.
Q. Have you reviewed any of the deposition testimony of the doctors who cared for Mrs. Knight?
A. No, I did not.
Q. And do you know what dose of Pradaxa Mrs. Knight actually used?
A. I have information that she was on the 75-milligram dose. At least that's what was relayed to me from the -- the lawyers in the case.
Q. Okay. Given that you've not reviewed the medical records in the case or reviewed any of the testimony from the case, you don't have a sense of what Mrs. Knight did or didn't understand about the risks of Pradaxa when she took it, do you?
A. No. I have not had a conversation, and it's my understanding she died, so I couldn't have one now either.
Q. Okay. And you also have no understanding of what Mrs. Knight's doctors, the doctors who cared for her and prescribed her Pradaxa, you have no understanding of what they did or didn't understand about the risks of Pradaxa, correct?
A. No. But I believe that some of those treaters are going

to be testifying or provided deposition testimony, so I -- that's not something that I covered in my scope of the work that I did.

Q. And just to follow up on that scope point, some of the criticisms that you've raised about the Medication Guide for Pradaxa, you're not able to tell the jury, for example, that any one of those specific issues would have affected Mrs. Knight's specific care or her treatment or her course on the medicine, correct?

A. I haven't looked to see if those questions have been asked of anyone, but -- so I can't answer that. I don't know.

Q. Okay. And you talked a little bit about patients who, in your view, when they're on Pradaxa can either be too high or too low, correct?

A. In blood levels?

Q. Yes.

A. Yes, that's correct.

Q. You don't know one way or the other whether Mrs. Knight would have fallen at either end of that spectrum, correct?

A. Well, I think I can predict, based on what I do know, the little bit that I do know about her. But I haven't seen -- I don't believe she had her blood level measured, so I can't tell what it was.

Q. And what you know about her is not based on actually

reviewing her medical records, correct?
A. No. I've not reviewed her medical records. That's what I have seen as sort of the summary of her condition.
Q. Okay. Something you learned about from the lawyers?
A. Yes, and also some slides from the opening.
Q. Okay. You are not giving an opinion in this case on topics like what led to Mrs. Knight's GI bleed or what led to her passing, are you?
A. No. I think you're saying a causation -- a specific cause, and no, I'm not. A physician will be doing that. That is not my role.
Q. Okay. I wanted to actually go back to the topic that you started with with Mr. Moskow on the topic of the 75-milligram dose of Pradaxa. And I mostly wanted to just make sure that we were clear on some basic facts about that dose of the medicine.
You understand that when Boehringer Ingelheim submitted an application for approval of Pradaxa for patients with atrial fibrillation, the company proposed two doses, correct?
A. Yes.
Q. They proposed a 150-milligram dose and a 110-milligram dose, correct?
A. Yes. That's what was tested in RE-LY.
Q. And you were anticipating my next question.

Those were the doses that had been tested in terms of the patients on Pradaxa in the RE-LY study, correct?
A. Yes.
Q. There were not patients in the RE-LY study who took 75 milligrams of Pradaxa, correct?
A. Yes, exactly.
Q. And there were not patients in the RE-LY study who had severe renal impairment, correct?
A. Yes. There were a couple I think that slipped through. But, you're right, it was not a -- they were trying to exclude patients with severe renal impairment in the study.
Q. And both of those facts, that the RE-LY study did not test the 75-milligram dose and that there were not patients with severe renal impairment in the RE-LY study, those were facts that the FDA were fully aware of, correct?
A. Yes, they were.
Q. Now after the study was done, the FDA agreed to approve a 150-milligram dose of Pradaxa for atrial fibrillation, correct?
A. Yes.
Q. But the agency made the decision not to approve the 110-milligram dose. Do you recall that?
A. Yes, that is correct.
Q. Okay. And because they weren't going to approve the lower dose of Pradaxa, do you recall seeing in the review

memos for Pradaxa that the FDA actually specifically said we need to have a lower dose for patients who have severe renal impairment?

A. Yes. That was talked about in the summary review.

MS. JONES: Okay.

(Pause in proceedings.)

MS. JONES: While she's doing that, may I approach and hand the witness the document?

Okay. Dr. Plunkett, I have handed you what's been marked for identification as Defendant's Exhibit 5827.

Q. Do you recognize that document?

A. Yes, I do.

Q. Do you recognize it as the summary review by the FDA for Pradaxa for the atrial fibrillation application?

A. Yes, that's correct.

Q. Okay.

MS. JONES: Your Honor, we would move for the admission of 5827.

MR. MOSKOW: No objection.

THE COURT: It is admitted, and it may be published.

(DEFENDANT'S EXHIBIT 5827 ADMITTED INTO EVIDENCE.)

MS. JONES: Dr. Plunkett, let's just look at this document in a couple of places if we could.

So if you turn to just the first page of the document, up at the top of the page there is a reference to

the Center for Drug Evaluation and Research.
Q. Do you see that?
A. Yes.
Q. And that's a part of the FDA that is specifically devoted to, among other things, evaluating new drug applications for prescription medicines, correct?
A. Yes, that is correct.
Q. And the FDA has different centers that focus on different types of products; is that right?
A. That's correct.
Q. Okay. And if we turn to the second page of Exhibit 5827, you see there's a heading there to the deputy office director decisional memo.
A. Yes.
Q. Do you see that?
And there's a date of October 19, 2010, correct?
A. Yes.
Q. And then if you look a little further down, you can see that the memo is from someone named Ellis Unger, M.D., deputy director. Do you see that?
A. Yes.
Q. Do you have an understanding who Dr. Unger is?
A. Yes. He was the -- well, at that time he was part of the -- ODE is Office of Drug Evaluation 1. And within that, there is a division that was looking at cardiovascular renal

drugs, and he was the deputy director of that OED-1, so the senior level within that drug evaluation review group.

Q. And so if you look a little further down, you can see there's a reference to the name Pradaxa, correct?

A. Yes.

Q. And then the approved indication is described there. Do you see that?

A. Yes.

Q. And it says: For reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

That just means this is a medicine that has been proposed for patients who have AFib and who need stroke protection, correct?

A. Yes, that's correct.

Q. Okay. And then there is a reference there to action, correct?

A. Yes.

Q. And that's the place where Dr. Unger indicates what the FDA intends to do based on his review of the data that was submitted as part of the application, correct?

A. Yes, that's correct.

Q. And what it says here is what you just finished telling us all, that the FDA approved the 150-milligram strength, correct?

A. Yes.
Q. And decided not to approve the 110-milligram strength, correct?
A. That is correct.
Q. And then at the bottom of that page, there is a listing with the heading of Material Reviewed and Consulted. Do you see that?
A. Yes.
Q. What's that list?
A. That's a list of all of the documents that were provided by different parts of the review division, and it lays out sort of their review of the data. So like, for example, I can go to the FDA website, and I can find each of these documents.

And I did do that to take a look at what was said by different parts of the review group. I didn't look at the CMC, but I did look at the medical officers, the pharm tox, the clinical pharm, things like that.
Q. And so these are all doctors and scientists and subject matter experts at the FDA who collectively in different teams looked at different parts of the medicine, correct?
A. Yes, that's correct.
Q. And various of these individuals actually prepared memos reflecting their analysis of their subject matter area and explaining their conclusions, correct?

A. Yes.
Q. And by my count, there are about 33, 34 folks who are listed here on this list. Is that a reasonable estimate just eye-balling it?
A. Yes.
Q. Okay. And if you look at the different subject matter areas, you mentioned there is pharmacology toxicology, there is a statistical review. You see that?
A. Yes.
Q. Okay. And there's clinical pharmacology, correct?
A. Yes.
Q. All right. And various other areas that looked at the Pradaxa application.

Let's turn to page 3 of Exhibit 5827. And we're not going to go through this entire document, but just to orient ourselves here, there is a section that is entitled Action.

Do you see that?
A. Yes.
Q. And it says: The Division of Cardiovascular and Renal Products is recommending approval of dabigatran etexilate, 150-milligram capsules for oral administration, for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. And then in parenthesis, it just says AF, correct?
A. Yes.

Q. And then it goes on to say: I concur with their recommendation for approval, right?
A. Yes.
Q. And then they say we're not going to approve the 110-milligram strength of the medicine, correct?
A. That's the next two sentences, yes.
Q. Then if you turn back to page 16 of the exhibit, there is a paragraph at the bottom that is focused specifically on consideration of renal insufficiency.
Do you see that?
A. Yes.
Q. And renal insufficiency is just another way of saying patients who have bad kidneys, correct?
A. Right. Kidneys aren't working properly.
Q. Right.
And that's the category of patients that you have spent some amount of time describing today, correct?
A. Yes.
Q. All right. And just to situate ourselves here, it starts out by saying: In not approving the 110-milligram strength, dosing options were limited for patients with severe renal insufficiency.
And that just means when the agency decided they weren't going to approve the 110, that meant there weren't -- there wouldn't be an option for patients whose kidneys were bad,

correct?
A. Yes, that's correct.
Q. And it goes on to say: The division concluded that it would be desirable to provide access to dabigatran for this patient population.
Do you see that?
A. Yes.
Q. And the reference to dabigatran, that's just another reference to Pradaxa, correct?
A. Yes.
Q. And so do you understand it to be the case that it was the Division of Cardiorenal Medicines that determined that it would be a good idea for patients who have severe renal insufficiency to have access to Pradaxa?
A. They have certainly -- that is what they are laying out in this document, yes.
Q. Okay. You agree that that's what happened, correct?
A. Yes. That is what happened, that's true.
Q. It goes on to say: Based on pharmacokinetic modeling, comparing pharmacokinetic data from RE-LY with data from a small study of subjects with compromised renal function, a dosing regimen of 75 milligrams BID appears appropriate for patients with estimated creatinine clearance of 15 to 30 milliliters per minute.
Did I read that correctly?

A. Yes, you do. I'm sorry. Yes, you did.
Q. Thank you.
And that reference there to 75 milligrams BID just means twice a day, correct?
A. Yes.
Q. And what that is telling us is that the FDA conducted its own pharmacokinetic modeling, it compared some of the universes of data that it had, and it determined that a 75-milligram twice a day dose would be appropriate for patients who had severe renal impairment, correct?
A. That is correct. And I believe that's what we talked about this morning.
Q. That was not modeling that was done by Boehringer Ingelheim, correct? The FDA relied on its own modeling, correct?
A. Yes, they did. And I think I told you even which study it was. It was a small study, but yes.
Q. It was a Phase I study, correct?
A. That's correct.
Q. Okay. It goes on to say: The 75-milligram strength is already manufactured by the applicant and marketed in the EU and can be marketed in the U.S.
Did you know that there -- I think I'm back.
Did you know that the 75-milligram dose was approved for treatment of patients who had VTE issues in Europe?

A. Yes. It was a different indication, so different length of time. But, yes, it was approved in that population in Europe.

Q. Okay. That paragraph concludes by saying: Patients with creatinine clearance greater than 31 milliliters per minute should receive the 150-milligram BID.

Which just means twice a day, correct?

A. Yes.

Q. That is the higher dose of Pradaxa, correct?

A. Yes.

Q. Based on data from one subject who received hemodialysis, dabigatran appears dialzyable, but there are not sufficient data to make any dosing recommendation in the dialysis population.

So patients whose kidney functions had become so problematic that they had to have dialysis, they were excluded from treatment with Pradaxa, correct?

A. Based upon the label, yes, that's true.

Q. Okay. Did you know that when BI submitted the original proposed labeling for Pradaxa to the FDA, that the company actually proposed that patients with severe renal impairment shouldn't receive Pradaxa?

A. Yes.

Q. Okay. And you've seen those specific documents?

A. Yes.

Q. And the company submitted a label, and the FDA actually sent something back striking out what the company had written?

A. Yes.

Q. You remember that?

So the idea of patients with severe renal impairment getting Pradaxa, that was not Boehringer Ingelheim's idea, correct?

A. If you're asking me the change to the 75-milligram dose, I would agree that was not theirs. But they actually -- in some of these documents they were pushing for the use of the 110 dose.

Q. Well, you understand that the FDA didn't approve the 110 dose, correct?

A. Yes, I do.

Q. And you understand I'm asking you about the 75-milligram dose, correct?

A. Yes, I do.

Q. Okay. And it is sounds like you understand that Mrs. Knight took the 75-milligram dose?

A. I do.

Q. Okay. I just wanted to get us on the same page.

And let me go back to my original question, the idea of patients with severe renal impairment getting Pradaxa, that was the FDA's idea originally, correct?

A. Getting any Pradaxa? I don't know that that was their idea. Certainly the issue of the 75-milligram dose, yes, I agree with that. That was the FDA's idea as a way to solve the problem.

Q. Okay. The FDA also viewed it as a priority that patients who had severe renal impairment would have access to Pradaxa, correct?

A. I don't know about the word priority, but certainly it was something that they were looking for. So if you read this review memo, that's what they lay out.

Q. When FDA approved the 75-milligram dose of Pradaxa, do you agree that that reflects that the FDA's judgment that the 75-milligram dose of Pradaxa was safe and effective for patients who would take it?

A. Well, I can't get in the mind, I didn't see them state it quite that way. But I would assume that they did believe it would be -- would be safe and effective to be used that way, yes, based on the fact that they made that decision for the labeling.

Q. And, in fact, if I recall your direct examination testimony, you testified that whenever the FDA approves a medicine for use, that reflects its judgment that the medicine is safe and effective for whatever the patient population is, correct?

A. Yes. That's why I answered that way. I'm assuming that

is true based upon my understanding of the way the process happens.

I guess, in that approval document, they didn't state it quite that way. But I would agree that that is the standard they use.

Q. And you have no reason to doubt that the FDA believed that, correct?

A. I don't, no.

Q. Let me see if I can just ask you a couple of simple questions now that we have gotten the facts established.

Do you believe that the FDA was wrong when it decided that a 75-milligram dose of Pradaxa should be available for patients with severe renal impairment?

A. No, I have not formed that opinion.

Q. Do you take issue with the modeling that the Food and Drug Administration did to support its decision to approve the 75-milligram dose of Pradaxa for patients with atrial fibrillation?

A. So what do you mean by take issue with? You mean do I agree with everything --

Q. Let me state it more simply.

A. Okay.

Q. Do you think they got it wrong?

A. I don't think -- no, I don't think they got it wrong, but there are issues with it that the company pushed back on

that I'm aware of.

Q. Well, that -- I'm not sure I understand what the last part of the answer means.

Was the answer to my original question, no, I don't think they got it wrong?

A. I haven't formed that opinion, that is true.

Q. Now, you have said if I --

MS. JONES: I'm sorry. Mr. Reynolds, we can take down this document.

Q. You've said that the fact that the 75-milligram dose was approved for patients with severe renal impairment, that that creates a safety issue in your mind.

A. Yes.

Q. I believe the way you described it was that it meant that patients who were taking the 75-milligram dose in the United States are being treated like guinea pigs.

Is that the way you described it?

A. Yes, that's true.

Q. And that's a serious claim to make. You understand that, right?

A. Absolutely, yes.

Q. Okay. Have you communicated your view that there is a serious safety issue created by the fact that there are patients taking the 75-milligram dose, have you communicated that view to the Food and Drug Administration?

A. No, I have not.
Q. Okay. You interact with the FDA as part of your consulting work; is that right?
A. Yes, I do.
Q. In any of those interactions, have you ever conveyed to the FDA that you believe that there is a serious safety issue created by the fact that the 75-milligram dose of Pradaxa is available to patients who have severe renal impairment?
A. No. And I've not worked on Pradaxa with the company with the FDA.
Q. So that's a no, you have never --
A. Yes. No, I have not. That's correct.
Q. Now, Dr. Plunkett, you have told us some about your background and what your work is. But just to be clear, you are not a medical doctor, correct?
A. That's correct, I am not.
Q. And what that means as a practical matter is you don't diagnose or treat patients with any medical condition, correct?
A. That is correct, I do not.
Q. And that means you don't treat patients who have atrial fibrillation, correct?
A. I do not.
Q. You don't treat patients who might have a bleed while

they're on an anticoagulant, correct?
A. I do not.
Q. All right. And that means you've never been responsible in the real world for communicating the risks of a medicine to a patient, correct?
A. That's true. I'm not a physician.
Q. When you leave the courthouse either tomorrow or sometime later in the trial, we'll see how we do on time, it won't be to go back out into the world and actually care for patients who struggle with some of the conditions that the jury will hear about throughout the course of the trial, correct?
A. Not as a treating physician or a nurse. No, I don't do that.
Q. Well, you won't be caring for patients in any capacity because you're not a medical professional, correct?
A. That's correct.
Q. And, in fact, what you do as a major part of your livelihood is what you've done today, which is to come into court and to testify as a paid expert on behalf of plaintiffs lawyers, correct?
A. Yes. We talked about that.
Q. Okay. And I think you said that that was 50 percent of your income; is that right?
A. On an average over the years, yes.

Q. Okay. And if you stopped doing that, that would be a major loss of income. Is that fair to say?
A. It's possible, yes.
Q. Okay. You've testified in court or in a deposition over 150 times; is that right?
A. Yes, that's correct.
Q. Okay. And by my count, you've offered testimony as a paid expert for plaintiffs lawyers at trial to more than 30 different juries around the country; is that right?
A. Ah, yes. I think I said maybe 50, but if it's 30, I'll take your word for it.
Q. Okay. Well, you would know better than I would.
And that's all over the country. You travel around to do that, correct?
A. I've been in different venues, yes, that's correct.
Q. Okay. And just last year alone, 2017, you went under oath as an expert witness 24 different times. Does that sound right to you?
A. Yes. Last year was a very busy year.
Q. Okay. And collectively through that testimony working for plaintiffs lawyers, you've earned millions of dollars giving that testimony reaching back a decade or so, right?
A. Going back about 15 to 20 years, yes, that's true.
Q. Okay. Now you talked a little bit about your clients, who some of your clients are. But when you do what you're

doing today, you're getting paid by plaintiffs lawyers, correct?

A. In the area of product liability, yes --

Q. Yes.

A. -- that's true.

Q. I mean, the millions of dollars that we were just talking about, that's money you've made working for plaintiffs lawyers, correct?

A. Not all of it, but yes. A lot of it has been, yes.

Q. Okay. And by my count, again just since 2007 if we -- since 2010, there have been approximately 20 different products that you've testified about on behalf of plaintiffs lawyers. Does that sound right to you?

A. Yes, that's probably true.

Q. Okay. Pradaxa is one of those, and you've made $135,000 in this litigation alone; is that right?

A. Not just this case, but over six years working in this general area, yes.

Q. Okay. And you are not just working for plaintiffs lawyers in litigation involving Pradaxa. You're also working for plaintiffs lawyers in litigation involving Xarelto, one of the other novel oral anticoagulants, correct?

A. Yes. It has its own unique issues.

Q. Okay. And, in fact, just last month you were in a

courtroom, sitting in front of a jury offering paid testimony as a litigation expert, correct?

A. An expert in pharmacology and toxicology, yes.

Q. Okay. And that medicine is made by different companies, correct? It's not made by BI, right?

A. That's correct. It's a competitor to Pradaxa.

Q. All right. And you said that it's got its own issues. But, in fact, you've made some of the same criticisms there that you've made with respect to Pradaxa, correct?

A. Some of them are the same, some are different.

Q. So, for example, in your report in your deposition in the Xarelto litigation, you gave the opinion that the FDA-approved label for Xarelto was inadequate, correct?

A. Yes. Generally it has inadequacies.

Q. Just like you've done here, correct?

A. Yes, that's true.

Q. All right. And you criticized Xarelto in your report for not having blood monitoring, correct?

A. Yes.

Q. Okay. And you criticized Xarelto in your written report in that litigation for inadequately warning about the risk of bleeding in older patients, correct?

A. Yes.

Q. And you were paid in that litigation, too, just to be clear?

A. Yes. I was working on behalf of injured parties.
Q. Okay. Did you know that some of the same lawyers that are suing BI in this litigation are also suing the makers of Xarelto?
A. I'm working for different ones, so I don't know. It's possible, but the ones that I'm working with are a different set.
Q. Okay. So you've mentioned a couple of medicines where you've been involved in litigation related to them. One was Vioxx, and the other one was Risperdal.
Do you remember that?
A. Yes.
Q. And I think you said Vioxx was taken off the market, and the labeling for Risperdal, that was changed.
Do you recall that?
A. It has been changed several times, but yes.
Q. Okay. And you're not testifying under oath to the jury that your work as a litigation expert was the reason for any of those things, correct?
A. I'm not. In fact, I pointed that out, I believe, in my testimony. I said I'm not saying that it was what I did. It is just that what I testified about is consistent with what changed.
Q. Okay. And in both of those circumstances, again, you were paid by plaintiffs lawyers to offer criticisms of the

way that the company had conducted itself, correct?
A. Yes. I was working on behalf of injured parties in those cases as well.
Q. Okay. And just to be clear, there were plenty of medicines where you've become involved in litigation working with plaintiffs lawyers, and the label does not change, correct?
A. Some of them, that's true, yes.
Q. For example, in the Pradaxa litigation, you've testified about various issues with the Pradaxa label. There have been no changes required by the FDA to the Pradaxa label, correct?
A. The changes we're discussing here, those have not happened yet, that's true.
Q. There have been no changes to the Pradaxa label as a result of your testimony, correct?
A. Well, none of them would be the result of my testimony. I've said that. There have been changes that have been consistent with my testimony in some cases. But I agree, I am not the impetus that is making FDA or the company specifically make a specific change, no.
Q. And the same situation with respect to Xarelto. Xarelto is another medicine that was approved by the FDA without blood monitoring, correct?
A. That is correct.

Q. And you've criticized the makers of Xarelto because you've said they ought to be encouraging blood monitoring, correct?

A. Yes. They have information and data to indicate the drug would be safer if they were -- and actually it's not so much blood monitoring there. It's not the same, it's a little different issue. But essentially it's exposure assessment, yes.

Q. Okay. And you've used phrases like exposure and exposure assessment in this litigation, too, haven't you?

A. Yes, but it's a different test that I am advocating for in Xarelto versus here.

Q. In that litigation, you are talking about the PT test, right?

A. Yes.

Q. Okay. And what test is it precisely that you're arguing to be used for Pradaxa patients?

A. It's actually a measurement of the level of Pradaxa in the blood is the one that I've discussed. Although there are -- in the label, I've talked about the fact that there are other tests available that could be used. But I've been specifically talking about measuring blood levels.

Q. Right. But you understand that there has to be some kind of test, there are different tests that are sometimes used for evaluating things that are in the blood.

Is there a specific test that you're suggesting?

A. I'm suggesting measuring the level of the drug in the blood, and that can be done at laboratories in the U.S.

Q. Well, let me ask you another question.

You have shown the jury documents that refer to things like the aPTT and the ECT and the dTT. Those all sound familiar to you?

A. Yes. We talked about that in some of the -- in the CCDS, the core company data sheet, yes.

Q. Are you taking the position that any one of those particular tests need to be used with Pradaxa specifically? Or you haven't gotten that far?

A. So I haven't particularly pointed to one specific test because I believe the issue is actually monitoring the levels. But certainly those tests, as I've talked about in other situations -- not with you, but with others -- there are correlations with some of those tests where you can look at the upper limit. There's information in the European label that would be useful also to provide to doctors in the U.S. Some of that information in the European label would be useful for doctors.

It talks about the dilute thrombin time. There is others as well. Do you want me to -- we didn't discuss that here because we have talking about the Medication Guide, which has no similar discussions in it.

Q. My only question was, is there a particular test that you've taken a view in this litigation doctors should be using to measure blood levels for Pradaxa?
A. And I answered that. I said I believe it should be actually measuring the levels of the drug in the blood.
Q. You understand that there are specific types of tests, that it's not just you take a vial of blood and hold it up to the light, there is more to it that happens?
A. No, absolutely. I'm not -- I think you and I are crossing paths here.

I have a very specific opinion, which I've said, measure the level of Pradaxa in the blood, which can done in laboratories in the U.S. There are other tests which we talked about, INR, aPTT, ECT, dilute thrombin time, the hemoclot assay. The hemoclot assay with the dilute thrombin time is one that has been shown to be correlated with the levels of Pradaxa in blood. The aPTT, I talked about before, has been shown to be on the high end, at least able to identify people with excessive dabigatran exposure.

Any of that information passed on to physicians in the U.S. would be extremely important for them to be able to look at their patients. But am I saying it can only be this or only that? No, because the company hasn't even said that. In Europe, they give physicians options.
Q. Is the hemoclot approved in the United States as far as

you know?
A. No. Unfortunately they haven't gotten it approved here.
Q. Dr. Plunkett, I want to go back to this topic of the FDA's approval of the 75-milligram dose of Pradaxa, if we could.
Are you aware that after the FDA approved the 75-milligram dose of Pradaxa, it actually generated a memo, that there were members of the clinical pharmacology team who put together a memo describing their thinking on that dose?
A. I -- I may have seen what you are talking about. Maybe you could show me the document, and I could tell you if I've seen it or not. I've seen other discussions within the agency if that's what you mean.
MS. JONES: Okay. Well, I'm going to ask us to pull up 9328.
Oh, actually, let's not put it up on the screen just yet, Mr. Reynolds. Thank you.
May I approach, Your Honor?
THE COURT: Yes, you may.
MR. MOSKOW: I have no objection, to move things along.
THE COURT: All right. It's admitted and may be published.
(DEFENDANT'S EXHIBIT 9328 ADMITTED INTO EVIDENCE.)

MS. JONES: All right. Could we call that up, please, Mr. Reynolds?

Q. Dr. Plunkett, do you recognize this Exhibit 9328?

A. I'm not sure I have seen it in this form, no. I have seen some of these graphs before, but I don't know if I have seen the complete memo. I don't recall.

Q. Okay. Well, let's walk through it and see if it jogs your memory at all.

MS. JONES: If we could just call out the top part. Thank you, Mr. Reynolds.

Q. Do you see the date there of October 20th, 2010?

A. Yes.

Q. And you recognize that as the date that Pradaxa was approved in the United States for atrial fibrillation?

A. I believe it was the 19th, but this would have been the next day, yes.

Q. Okay. You're correct on that.

Okay. And you see the reference there to a memo from Abraham Karkowsky, the group leader for the division of cardiovascular and renal products? Do you see that?

A. Yes.

Q. And then that's a memo written to Dr. Ellis Unger. He is the deputy director we were talking about earlier today, correct?

A. Yes.

Q. All right. And Dr. Unger was the individual who wrote the summary review that included that description of why the FDA had decided to approve the 75-milligram dose of Pradaxa, correct?

A. Yes. There was more in it than that, but that was also discussed.

Q. Correct.

And if you look at the subject line of that memo, it said: Approval of a 75-milligram BID dosing regimen for subjects with severe renal dysfunction, and then in parentheses it just defines that category of patients by their creatinine clearance of 15 to 30 milliliters per minute, correct?

A. Yes.

Q. Okay. And we won't go through this in tremendous detail because we have touched on some of these points.

But you see in that very first paragraph, it says: The RE-LY study is the basis for the approval recommendation for dabigatran etexilate to decrease the risk of stroke and systemic embolic events in subjects with non-valvular atrial fibrillation.

Did I read that correctly?

A. You did.

Q. And then it goes on to say: In the RE-LY study, subjects with severe renal impairment, i.e. an estimated

creatinine clearance, creatinine clearance of 15 to 30 milliliters per minute, were routinely excluded from enrolling in the study.

And that is just that point we were talking about earlier. The FDA understood that patients with severe renal impairment weren't included in the RE-LY study, correct?

A. That is correct, Yes.

Q. Have you seen any documentation to suggest that the FDA ever suggested that that information needed to be included in the Medication Guide for Pradaxa?

A. That there were no patients within the study?

Q. No patients with severe renal impairment.

A. I haven't seen FDA suggest that, no.

Q. Okay. If we move down to the next paragraph, it says: For the RE-LY study, the decision to not include or to discontinue subjects with markedly decreased renal function was probably a rational decision.

Do you see that?

A. I see that, yes.

Q. Do you agree with that statement?

A. Yes, I agree that -- excluding them from the study, if that's what you are asking me, I believe that was a rational decision based on what we know about the drug.

Q. So you don't criticize BI for not having patients with severe renal dysfunction in the RE-LY study, correct?

A. Oh, no. I'm not criticizing them for that initial study, no.

Q. Okay. And then down at the bottom of the paragraph says: The decision not to enroll or to discontinue patients with severe renal failure in the RE-LY study, however, creates uncertainty about the magnitude of benefit or risk ratio for this population.

Did I read that correctly?

A. You did.

Q. Okay. And then if we flip over to page 3 of Exhibit 9328, do you see there is a discussion there of the specific modeling and simulation work that the FDA's clinical pharmacology team did to determine what dose of the medicine would be most appropriate for patients with severe renal impairment?

A. I see the paragraph, yes.

Q. Okay. And it says at the first -- at the top of that first paragraph: The clinical pharmacology reviewers performed simulation of various dosing regimens and proposed 75 milligrams once a day for subjects with severe renal impairment.

And that QD just means once a day, correct?

A. Yes.

Q. And so what that tells us is that when the FDA originally started considering how are we going to make

Pradaxa available to patients with severe renal function, their first thought was maybe the right dose is 75 milligrams once a day, correct?

A. Yes.

Q. Okay. And then it goes on to say: Upon further deliberations, the goal of the simulation exercise was revised to model a dabigatran regimen in severe renal dysfunction patients whose concentrations are reasonably similar to that expected in subjects with moderate renal impairment receiving 150 milligrams BID regimen.

Did I read that correctly?

A. You did.

Q. Can you tell us briefly what that means?

A. BID regimen --

Q. No.

A. -- or the whole statement?

Q. The statement, yes.

A. I'm sorry. Okay.

So if you read the first paragraph, and then you read the second paragraph, what they're saying is, is they are trying to match their computer modeling to the results from the RE-LY study because they did have people that had moderate renal impairment. So they took that small population, that smaller population from the RE-LY study of the 30 to 50, and they tried to match through modeling the

exposure they were getting.
Q. And do you recall seeing in the documentation on the subject of dosing for severe renally impaired patients that the FDA ultimately had the view that patients who had moderate renal impairment had done well on the outcomes in the RE-LY study, and that's why they were targeting or trying to match with those patients' exposure?
A. I don't know if I'm familiar with what you're referring to.
Q. Okay.
A. But certainly I agree that is what they did. And there's a publication that followed this in the published literature where some of this is also described.
Q. Yeah, I suspect we'll get to that tomorrow.
If you read the next sentence, I think it gets to the point that I was just raising.
This target was based on the fact that the 150-milligram BID regimen for those with moderate renal function impairment produces substantial benefit in the RE-LY study.
Did I read that correctly?
A. You did.
Q. Okay. And that's just the FDA saying that for folks who were on the 150 milligram twice a day, those people who had moderate renal function, it seemed to show substantial benefit in those patients, correct?

A. I agree that's what they have stated.
Q. Okay. And do you disagree with that statement by the FDA?
A. I wouldn't agree or disagree with that statement. I mean, it is what it is. I don't disagree that what their modeling showed.
Q. If you turn to page 4 of the document, just moving along quickly, do you see here that the FDA actually looked at three different dosing regimens for possible use with patients who had bad kidney function?
Do you see that?
A. Yes.
Q. And you see there is a reference to a 150 once a day. You see that?
A. Yes.
Q. And then they considered the possibility of 75 milligrams once a day. You see that?
A. Yes.
Q. And then they went on to say: The 75 milligram twice a day regimen in subjects with severe renal dysfunction is expected to provide 12-percent higher exposure with low peak to trough ratio compared to 150 milligrams BID in subjects with moderate renal dysfunction.
Now that is a discussion of the dose that the FDA ultimately approved for patients who had severe renal

impairment, correct?

A. Yes. This is the modeling they did with that dose.

Q. And what they said specifically was that they expected, based on their analyses, that there would be a 12-percent higher exposure to the medicine with patients who had severe renal impairment, correct?

A. I agree that's what they've stated.

Q. And so that was something that the FDA fully understood when it decided to approve the 75-milligram dose for patients with severe renal impairment, correct?

A. Based on their modeling, yes, that's what they were predicting.

Q. And when we see this word exposure, that is just another way of talking about blood levels, right?

A. They may actually be talking about area under the curve here. I'd have to look further at what they say. But certainly it's blood levels achieved over time, and they could be talking about total exposure. Or they could be talking about troughs versus peaks, and that's a specific blood level. I think they are talking about total exposure.

Q. Yes. Okay.

It goes on to say in that same paragraph: This clinical and clinical pharmacology reviewer did not consider the small increase in peak exposures on the 75-milligram BID regimen to be clinically significant.

Did I read that correctly?

A. You did.

Q. And that means that the FDA recognized the possibility of higher exposure for patients who had severe renal dysfunction if they were on the 75 milligram twice a day, but they didn't think that that was going to be clinically significant, correct?

A. Based on their modeling, that is true.

Q. If you turn to page 5 of that same document, that same FDA memo on the 75-milligram dose, underneath that image that appears there, there's a paragraph that begins the division concluded.

Do you see that?

A. Yes.

Q. And after they did all of their analysis, the FDA reported: The division concluded that the best tact is to assure that the population with severe renal dysfunction, not on dialysis, would have access to dabigatran.

Do you see that?

A. Yes.

Q. And that just means that the division, the cardiorenal division at the FDA concluded that the best approach for patients with severe renal impairment would be to make sure that they had access to Pradaxa, correct?

A. I agree that's what they've stated, yes.

Q. And do you disagree with the FDA's judgment on that issue?

A. I haven't formed an opinion one way or the other. I don't tend to try to second-guess what -- a decision FDA themselves has made. But I would disagree with the assertion that the modeling they did was, ah, predictive of what was actually occurring in patients.

Q. So you do take issue with the FDA's modeling and the ability of that modeling to predict patient experience?

A. Based on their own -- their own analysis and the company's own analysis and criticisms of the FDA modeling, yes. The company also criticized this modeling and talked about what it was missing.

So, yes, I believe there is limitations on what they did. And the biggest issue is they didn't test it in anyone actually that was AFib with severe renal impairment going forward. I just -- or letting doctors know that that information had not been -- had not been gathered.

Q. But this notion of testing, is that a criticism that you have of the FDA, that the FDA didn't immediately require testing of the 75-milligram dose?

A. No. It's the responsibility of the company at all times to do the testing.

So I am saying that -- I am saying that the company failed to test based upon knowing that it had no such data

even after the drug was approved.

Q. If we go further down in this paragraph, it says: A dosing regimen of 75 milligrams BID for this population provides reasonable matching of exposures to that expected with subjects with moderate renal dysfunction.

And that's just that idea that we were talking about earlier, that they were looking at patients with slightly better kidney function to see if they could match the level of medicine that they had gotten when they were in the study, correct?

A. Yes. Those people had a higher dose, but they were trying to match what they thought might happen, yes.

Q. And it goes on to say: A dose of 75 milligram BID was included within the label and will shortly be available for marketing. Since the variability was no greater than the population that was already studied, no monitoring of clotting effect was currently recommended.

Did I read that correctly?

A. You did.

Q. And that was the FDA's judgment at that time that it was not necessary that patients on the 75-milligram dose of Pradaxa receive blood monitoring, correct?

A. I agree, that's what it stated.

Q. The last thing I want to touch on as we finish up this document is this reference on page 6 of the memo from the

FDA up at the top.

It says: Since there is no empirical data on this population with regard to bleeding risk, particular attention post-marketing should be paid to bleeding and other safety events in those treated with the 75-milligram BID regimen in patients with severe renal impairment.

Did I read that correctly?

A. You did, yes.

Q. And as far as you know, you understand that the company, once it has a medicine approved, has an obligation to capture and report any reports that it receives of bad outcomes with the medicine, regardless of dose, correct?

A. Yes.

Q. Okay. And that would have been the obligation of the company with respect to the 75-milligram, correct?

A. Yes.

Q. And as far as you know, Boehringer Ingelheim discharged that obligation, correct?

A. If I discharge, do I know that they monitored? Yes. The adverse events, they did reporting. Yes, they did.

Q. That's the question.

MS. JONES: I think that's probably an appropriate breaking point, Your Honor.

THE COURT: All right. Ladies and Gentlemen, we'll adjourn for the day. I'd like you back here at 9:00 a.m.

tomorrow.

Remember my instructions before. Don't discuss the case or try to do any investigation or come to any conclusions on your own or together.

With that, I'll excuse you. We will see you back here at 9:00.

Dr. Plunkett, you can step down. Don't discuss your testimony with anyone. We'll see you back here at 9:00 tomorrow morning.

THE WITNESS: Thank you.

(Off the record.)

(Jury not present.)

THE COURT: All right. I just spoke with coach. He's got a game tomorrow at 7:30 in Welch, so we're going to adjourn tomorrow at like 4:00 --

MR. CHILDERS: That sounds great.

THE COURT: -- so that he can get to that game.

And, of course, some of the jurors asked earlier about Monday. The courthouse is closed Monday. It's a federal holiday. So we will -- as you already know, but I'll confirm it, we'll be closed.

I don't have anything else scheduled, so I'm comfortable with you folks, if you're comfortable, leaving anything you'd like here in the courtroom tomorrow at the conclusion. It will be locked, kept locked until you folks

show up on Tuesday. But I'll leave that up to you.

Is there anything else we need to address today?

If not, see you back here at 9:00 tomorrow.

MR. CHILDERS: Thank you, Your Honor.

MR. MOSKOW: Thank you, Your Honor.

THE COURT: Let me just have a bench conference with your folks up here just for a moment.

(Bench conference, not reported.)

(Proceedings were adjourned at 4:43 p.m.)

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CERTIFICATION:

I, Kathy L. Swinhart, CSR, certify that the foregoing is a correct transcript from the record of proceedings in the above-entitled matter as reported on October 4, 2018.

October 5, 2018
DATE

/s/ Kathy L. Swinhart
KATHY L. SWINHART, CSR